

A THESIS
on
THE NEUROGENIC ASPECTS OF THE AETIOLOGY
OF GASTRIC AND DUODENAL ULCERATION

submitted as part of the
qualification for the degree
of Doctor of Medicine of the
University of Edinburgh by

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C O N T E N T S.

	<u>Page.</u>
I PREFACE	1
II HISTORICAL	5
III THE NEUROGENIC THEORY	8
IV THE ANATOMY OF THE NERVOUS SYSTEM IN RELATION TO THE STOMACH AND DUODENUM.	12
1. The Vagus Nerves	14
2. The Sympathetic Nerves	20
3. The Intrinsic Nervous System of the Stomach	21
V THE PHYSIOLOGY OF THE STOMACH AND ITS NERVES	23
1. Local Physiology of Stomach and Duodenum	23
2. The Autonomic Nervous System	26
3. Special Points to note in the Anatomy and Physiology	28
VI THE IMMEDIATE CAUSES AND CONCOMITANTS OF GASTRIC AND DUODENAL ULCERATION.	30
1. The Acid Factor	30
2. Mechanical Factors	43
VII THE MORE REMOTE CAUSES AND CONCOMITANTS OF ULCERATION.	45
1. Extrinsic Factors in the control of gastric acidity	45
a. Nervous	48
b. Chemical	51
2. Acute Ulceration	54
3./	

3.	Other Theories and Factors in the aetiology of peptic ulcer.	59
a.	Infection	59
b.	Peculiarity of Blood Supply	60
c.	Chemical deficiency .	61
d.	Hypersensitivity . .	63
e.	Vitamin deficiency . .	64
VIII	AUTONOMIC IMBALANCE	65
1.	Experimental	65
a.	Animal Experiments . .	67
b.	Neurectomy Operations in man.	76
c.	The action of drugs .	83
2.	Spontaneous	87
3.	Acquired	99
a.	Organic Disease . .	99
b.	Tobacco Smoking . .	103
c.	Anxiety Factors . .	104
IX	PERSONAL EXPERIMENTS	106
1.	Estimation of Gastric Acidity	109
2.	Direct Vagal Stimulation .	123
3.	Experiments on Relative Over- action of the Vagus . .	135
	Protocols of Experiments .	147
X	CHRONICITY IN GASTRIC AND DUODENAL ULCER	154

	<u>Page</u>
XI CONCLUSIONS	168
XII REFERENCES	
a. Serial	172
b. Alphabetical	180

P R E F A C E .

When one considers the huge volume of work that has been done and the great number of writings that have been composed on the subject of gastric and duodenal ulceration, it may at first seem somewhat needless to burden library shelves still further with yet another thesis on this same subject. Nevertheless, in spite of all the work done from all aspects - anatomical, physiological, pathological, therapeutic, clinical, etcetera, - it still remains a fact that no general agreement has been reached as to causation or treatment, the whole subject being, as it were, something of a therapeutic and aetiological desert.

Still further research into the problem is therefore not amiss, so I offer no apology for having studied the literature, carried out experiments and set down my findings in a Thesis on The Neurogenic Aspects of the Aetiology of Gastric and Duodenal Ulceration, a thesis which I have the honour to submit as part of the qualification for the Degree of Doctor of Medicine of the University of Edinburgh.

Although the following pages contain numerous personal/

personal observations and experiences, I have found it necessary to include a considerable critical survey of the work of others; for however keen one may be to produce original work, when a subject such as this has been studied for a hundred years, it is impracticable and highly superfluous to go back and oneself start experiments ab origine, and one must therefore, after due consideration, take cognizance of the work of others. So my own attempts at adding something to the knowledge of this still chaotic subject, merely follow up the lead given by those whose writings I have freely referred to and expounded.

During the tenure of posts as Resident House Surgeon and Physician in the Royal Infirmary, Edinburgh, the Astley Ainslie Institution and the Victoria Hospital, Burnley, the last serving a wide industrial district of Lancashire, I was profoundly impressed by the great frequency of gastric and duodenal disorders, and the distress and economic wastage which they caused. Still more disturbing was the high recurrence rate in some types of gastro-duodenal disease even after the most skilful and orthodox treatment had been given. Two types were especially liable to prove recalcitrant to treatment, or to recur.

Firstly: Duodenal ulcers in young people, usually males, of age ranging from 20 to 40 years, with hypersecretion, hyperchlorhydria and no organic stenosis/

stenosis of the pylorus, and

Secondly: The gastric neuroses, so-called; cases with all the disabling manifestations of gastric or duodenal ulcer, with hypersecretion, hyperchlorhydria, disorders of motility of the stomach, but no ulcer either radiologically or at laparotomy.

All available treatment failed to give satisfaction either to patient or medical attendant, in a high proportion of these cases, whether it were strict medical treatment carried out for as long as economic conditions would permit, or partial gastrectomy, or gastroenterostomy, or even the most favourable of these, gastro-duodenostomy.

It was this problem in treatment then that proved the original stimulus for the investigations leading up to the writing of this thesis and it is mainly to these two types of disease that the work refers.

However, it would be too artificial if not impossible to divorce these from their close relation to other types of both gastric and duodenal ulcer, and my investigations have lead into a much wider field, and have touched on many parts of the whole tremendous subject of gastric and duodenal disease including the remote links in its aetiological chain.

The thesis does not purport to cover all the literature/

literature on the aetiology of chronic "peptic" ulceration, and indeed such an attempt has not been made.

(In 1911 Möller made a review of the literature and collected 325 references. (1) From that time till the present day, the number must have been quadrupled!)

I have, however, read most of the authoritative summaries of the subject and have selected but one main aspect - the Neurogenic one - because it is my opinion that with the data at hand, this interpretation of the aetiology offers a better explanation of all the varying manifestations of the disease than any other, and promises a more successful line of treatment than heretofore adopted. Whether the theory is correct only future work, experimental and therapeutic, can decide.

II. HISTORICAL.

That disorders of the stomach could be produced by morbid processes acting on distant parts of the nerves supplying that viscus is by no means a modern idea, for as far back as 1841, Carl Rokitansky describing erosions found post-mortem in the new-born associated with intracranial injury writes: "the proximate cause may be looked for in diseased innervation of the stomach, owing to a morbid condition of the vagus, and to extreme acidification of the gastric juice". Writing of another type of gastric erosion, which he clearly differentiates from normal post-mortem softening, he states that it "occurs, both in children and adults, as the sequel of acute affection of the brain or its membranes, and is probably brought about by a reflex action of the oesophageal and gastric branches of the vagus."(2)

Isolated in various parts of the medical literature of last century there must be many notes of cases in which the more than fortuitous association of gastric ulcer and disease of the brain had been noted. Thus in 1868, Hoffmann of Basle described a case of ante-mortem perforation of the oesophagus with peritonitis, in which a gummatous interpeduncular tumour with softening of the right half of the pons was found at autopsy $3\frac{1}{2}$ hours after death.(3)

In 1888 Arndt of Greifswald described ecchymosis of lower oesophagus and duodenum, with haemorrhagic erosions of the stomach in association with a median cerebellar tumour compressing the corpora quadrigemina and medulla. From this case and other information at his disposal he suggested that round ulcer is an angio-neurosis or trophoneurosis, an acute ulcer being considered the first stage of a chronic one.

The anatomical course of many of the nerves supplying the stomach had been worked out and most clearly described in the writings of Kollman (4), Swan (5), Gaskell (6), Langley (7) and others, and it is a pity that many of the authors of modern text-books of anatomy have seen fit to miss out these details. The clinicians however, seem to have looked on descriptions of the nerve supply of the stomach as so many isolated facts and not to have seriously implicated them in the cause of gastric disorder till Rössle in 1913 evolved his "Neurogenic Theory". He suggested that peptic ulcer was really a secondary disease (zweite Krankheit, he called it) produced reflexly through the vagus from some distant site where a primary disease (erste Krankheit) such as cholelithiasis or tuberculosis was operative. (8)

It was only with the conception of the ideas embodied in the working of an Autonomic Nervous System however that the first real impetus was given for looking/

looking further afield for the cause of gastric and duodenal ulcers than locally in the organs themselves. The credit must be given to Eppinger and Hess for their monograph on "Vagotonia" which has in truth proved a medical milestone. (9) Their ideas have been elaborated by many authors since that day and it is now recognised that imbalance in the Autonomic System may produce profound functional disorders of the gastro-intestinal tract and other regions.

The credit for formulating these ideas goes to von Bergmann (10), while Latarjet of Lyons (11) introduced the idea into France, and numerous authors, to mention only a few of the more prominent ones, Hurst of Guy's Hospital (12), McCrea of Manchester (13), Ryle of Guy's (14) and Harvey Cushing of Harvard (15), have written extensively on the subject for the benefit of the English speaking peoples.

III. THE NEUROGENIC THEORY OF GASTRIC AND DUODENAL DISORDERS.

The words "neurogenic" and "neurogenic theory" have been used frequently in the last few pages and it may not be quite clear what exactly is meant by them. "Neurogenic" of course, comes from *νεῦρον*, a nerve and *γενε*, birth. The Neurogenic Theory applied, as it is throughout this thesis, to the aetiology of gastro-duodenal disorders is, in its widest sense, the belief that these gastro-duodenal disorders are caused by abnormal conditions in some part of the body involving nerves which directly or reflexly lead to the stomach, and inducing in these nerves abnormal stimuli, which when conducted by them to the stomach promote abnormal conditions in that organ.

It would be useful here to anticipate somewhat the evidence brought forward later in the thesis, and to formulate here and now the working of the theory in its widest form.

It is conceivable that certain conditions operative in one part of the nervous system may make themselves felt in any other part of that system, but for our present purpose the nerve connections of the stomach may be affected in five distinct situations.

1. Centrally. The stomach is supplied by two sets of nerves only - parasympathetic (vagus) and sympathetic. Both these systems have their centre in the hypothalamus closely connected both anatomically and functionally with the cerebral cortex and "higher" centres on the one hand, and the unconscious or basal centres of the emotions, etc., in the thalamic region on the other. Thus:

(a) Stimuli arising in the cerebral cortex or thalamus may directly affect the autonomic centres and that effect be transmitted to the stomach.

(b) There are also vagal centres in the medulla, on the floor of the 4th ventricle, and both there and in the hypothalamus they are particularly open to the action of hormones or chemical substances in the cerebro-spinal fluid or the blood. The whole autonomic system conduction is carried out on a neuro-chemical basis and there is considerable evidence to show that pituitary, and probably other endocrine gland products exert a great influence on the state of the autonomic system.

2. In the direct nerve paths.

The stomach may be affected through abnormal conditions involving the vagus nerves in their course through/

through the body from medulla to stomach. Similarly may be involved the sympathetic system from the spinal cord, through the rami communicantes, the sympathetic trunk, the splanchnic nerves, the coeliac plexus to the peripheral gastric branches.

3. In the intramural course of the gastric extrinsic

nerves. Both vagal and sympathetic fibres run for variable distances in the wall of the stomach itself before ending, and are here particularly liable to be attacked by pathological processes in the stomach wall itself.

4. In the Intrinsic Nervous Mechanism of the Stomach.

The extrinsic nerves are only regulatory in their function and the stomach can both contract and secrete and does so automatically when completely cut off from external nervous connection. This power is thought to reside in the Enteric Plexuses of Meissner and Auerbach.

5. In the reflex nerve paths.

Chronic infective conditions in appendix or gall-bladder are known to influence gastric function. This is merely an illustration of how irritation of autonomic branches in a distant organ may be conveyed in a centripetal direction and then centrifugally to the stomach.

One point more has to be remembered especially. The stomach is supplied from the two parts of the Autonomic System, between which a balance is struck. Disorders of that system and of the organs it supplies may therefore arise in four ways:

- (a) By overaction of the parasympathetic, or
- (b) by underaction of the parasympathetic,
- (c) by overaction of the sympathetic, or
- (d) by underaction of the sympathetic.

Roughly speaking overaction of the parasympathetic simulates underaction of the sympathetic while underaction of the parasympathetic is simulated by overaction of the sympathetic.

Before understanding the working of this theory in practice or being able to demonstrate its tenability or truth, it is necessary to enquire into numerous subjects amongst which are the accurate anatomy of the gastric nerve supply, gastric physiology and pathology. These subjects will now be dealt with one by one.

IV. THE ANATOMY OF THE NERVOUS SYSTEM IN
RELATION TO STOMACH AND DUODENUM.

It is surprising that the ordinary anatomical text books are either very vague, inaccurate or almost entirely lacking in their accounts of the detailed nerve supply of the stomach, accurate knowledge of which is so important and indeed indispensable in the understanding of the true aetiology of many gastric disorders and in their rational treatment. I therefore dissected numerous human specimens obtained in the Anatomy Rooms or directly from the Post-mortem on suitable cases, to find out the true state of affairs.

In some 16 of these dissections I found the course and arrangement of the nerves to be remarkably constant. For those nerves and branches which are generally known and described in the current anatomical text books, the terminology used is that of the Birmingham Revision of the Basle Nomina Anatomica. For the other branches, simple directional or regional names have been applied.

The entire nerve supply of the stomach may conveniently be described under 3 heads:

1./

- | | | |
|----|---------------------|--------------|
| | (Parasympathetic) | |
| 1. | (Cholenergic or) | |
| | (Vagal.) | |
| | | } Extrinsic. |
| 2. | (Sympathetic or) | |
| | (Adrenalergic) | |

3. Intrinsic - a yet ill-defined system consisting of the so-called plexuses of Meissner and Auerbach, and ganglia and fibres connected with the vagi and perhaps the sympathetic also.

THE VAGUS NERVES.

The highest vagal centre is in the hypothalamus of which it occupies the supraorbital region, that is, the part situated above the optic chiasma and in front of the tuber cinereum (16) (17). From this centre fibres travel within the substance of the brain to the lower medullary nuclei - the Dorsal Nucleus and the Nucleus Ambiguus.

The vagus nerve proper arises in the medulla oblongata from the Dorsal Nucleus which is motor, secretory and sensory. Secretory and motor fibres to the Stomach arise in the motor part of the Dorsal Nucleus and pass forwards and laterally to emerge on the side of the medulla through the spinal tract.

Sensory fibres arise in ganglia placed on the glosso-pharyngeal and vagus nerves at the base of the skull (Jugular and Nodosum). Each fibre at once divides into a central and peripheral branch. Peripheral branches run outward in the nerves. Central branches run inward alongside the motor fibres, pierce the spinal tract of Trigeminal V, and enter the substance of the medulla.

Communications: The nucleus is connected with the other vagal nuclei. These nuclei in turn are connected with the nuclei of other cranial nerves by the medial longitudinal bundle. Motor parts of the nuclei/

nuclei receive fibres from the opposite pyramid. Sensory nuclei send fibres across to the opposite spino-thalamic tracts and medial lemniscus and they carry those fibres to the thalamus; new fibres arise in the thalamus and pass to the hypothalamus and the sensory area (post-central gyrus).(18)

From right and left jugular foramina the corresponding vagus nerve descends through the neck in the carotid sheath. It descends in the superior mediastinum and reaches the back of a bronchus where it breaks up into a simple network called the Posterior Pulmonary Plexus. From that plexus it emerges as one or more cords which pass to the oesophagus - the left on the front, the right on the back. So much is generally known and recognised and I have observed it many times in the Dissecting Rooms.

My own particular dissections show that the nerves now break up again into a simple network, called the Oesophageal Plexus, around the oesophagus in the posterior mediastinum. From that plexus two bundles emerge on front and back of oesophagus - the Anterior Gastric Nerve and the Posterior Gastric Nerve respectively. The anterior nerve is composed mainly of fibres of the left vagus but also contains a very considerable number of right vagal fibres which join it in the oesophageal plexus. Similarly the posterior gastric nerve contains fibres of both right and left vagus/

vagus. This has been checked by degeneration methods in the cat. (McCrea (19))

Ambiguity of former anatomical terminology, and neglect of the obvious implications of the oesophageal plexus have therefore been responsible for the inaccurate and misleading statement so frequently made that the left vagus supplies the anterior surface of the stomach and no other part of that organ while the right vagus is the nerve of the posterior surface.

Either of the gastric nerves may consist of 1 to 3 cords lying parallel to each other, and in this fashion they enter the abdomen through the oesophageal opening of the diaphragm, the one directly anterior, the other posterior to the oesophagus. As they enter, or immediately afterwards, both nerves incline slightly towards the right margin of the oesophagus though they still remain in close contact with that viscus.

Thus, when the cardiac end of the stomach is reached, the one nerve is lying directly anterior to the other at the edges of the lesser curvature, the crown of which, as it were, separating them.

Branches of The Anterior Gastric Nerve.

1. To Cardia, coming off while still in thorax, and also at the hiatus in the diaphragm.
2. To both sides of the true fundus of the stomach coming/

coming off at the point of entry of the main nerve into the abdomen.

3. At the cardia or very shortly afterwards, the nerve becomes three deviating branches (B.R. Anterior Gastric Plexus).

(a) A fine nerve runs to the right high up in the lesser omentum to the Porta Hepatis where some fibres turn into the liver. The remaining fibres descend in the free border of the lesser omentum in the front boundary of the opening into the lesser sac of the peritoneum and straddle the pyloric region, branches passing into the substance of the pylorus, into both sides of the 1st part of the duodenum, and both sides of the pyloric canal of the stomach.

We may call this the Right Branch of Anterior Gastric Nerve or Hepatic Branch.

(b) The direction of the main nerve is continued by the Middle Branch of the Anterior Gastric Nerve. It runs between the layers of the lesser omentum close to the Lesser Curvature and ends by passing into the substance of the anterior wall of the stomach at the Incisura angularis. In its course down the curvature it sends branches to the adjoining parts of the anterior aspect of the stomach, i.e. mainly to the outside of the Magenstrasse. It also sends a few short branches to join up with the corresponding branch of the Posterior/

Posterior Gastric Nerve which follows a like course only more posteriorly.

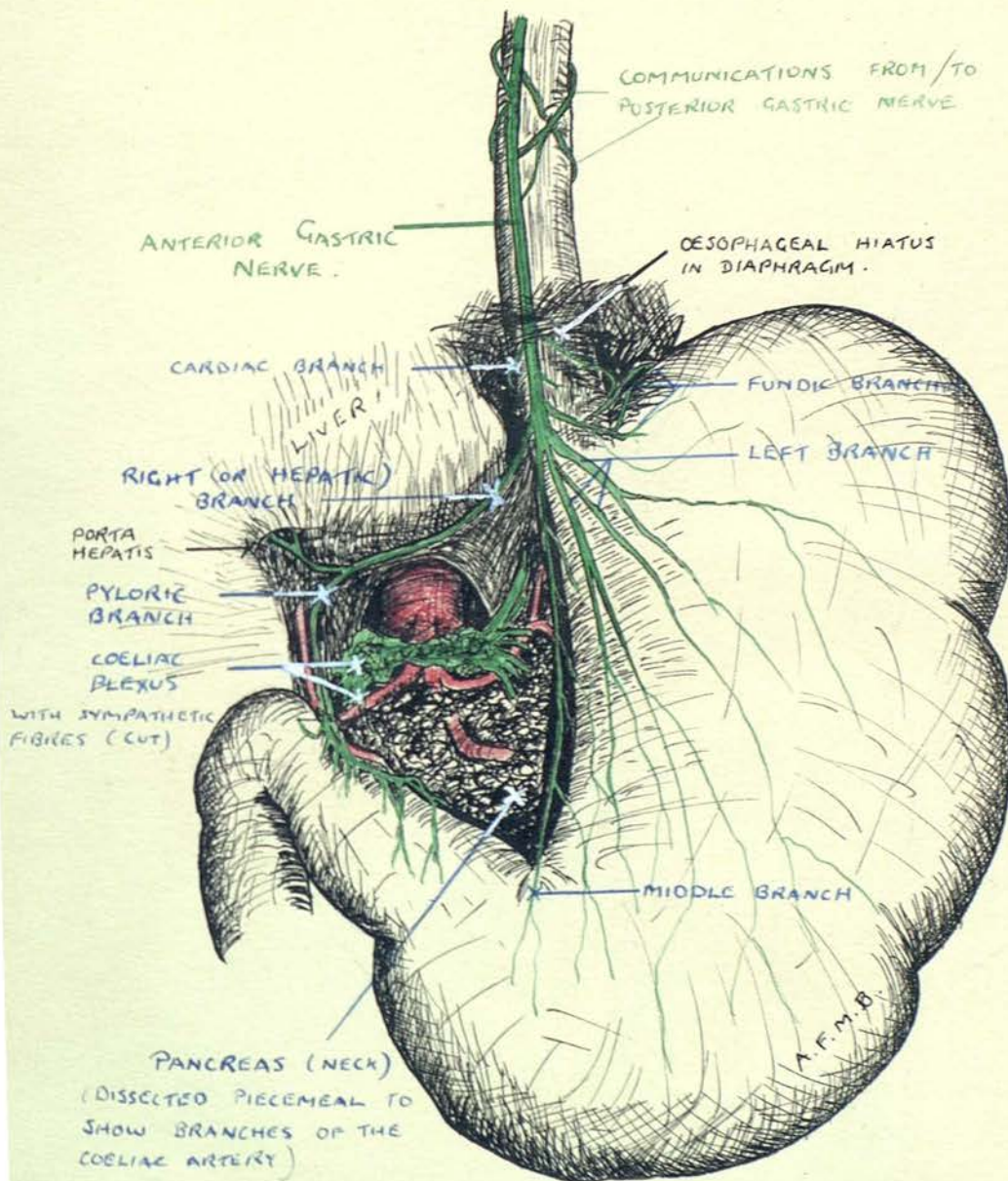
(c) The thickest branch or bundle is termed the Left Branch of the Anterior Gastric Nerve. It also separates off at or near the cardia and immediately passes, nearly vertically downwards over the anterior side of the stomach, branching and rebranching, and is thus scarcely related to the lesser curvature at all. (Fig. 1)

Branches of the Posterior Gastric Nerve.

1. Branches to Cardia coming off in thorax or at diaphragmatic hiatus.
2. At the cardia, this nerve also divides into three main branches but their distribution is different (B.R. Posterior Gastric Plexus).

(a) Right Branch. A thick nerve representing about $\frac{3}{4}$ of the fibres of the main trunk, turns quickly to the right, downwards on crus of diaphragm, gives a fine branch to the pancreas and enters the coeliac plexus. Its fibres may be traced macroscopically through the midst of the plexus and on the whole they do not appear really to take part in that plexus. Most of the fibres gain the base of the Mesentery and are presumably distributed to the small intestine, suprarenals, etc. A few fibres however, accompanied by numerous/

FIGURE 1.



A SKETCH FROM A DISSECTION TO
SHOW THE BRANCHES OF ANTERIOR
GASTRIC NERVE (O.T. LEFT VAGUS)

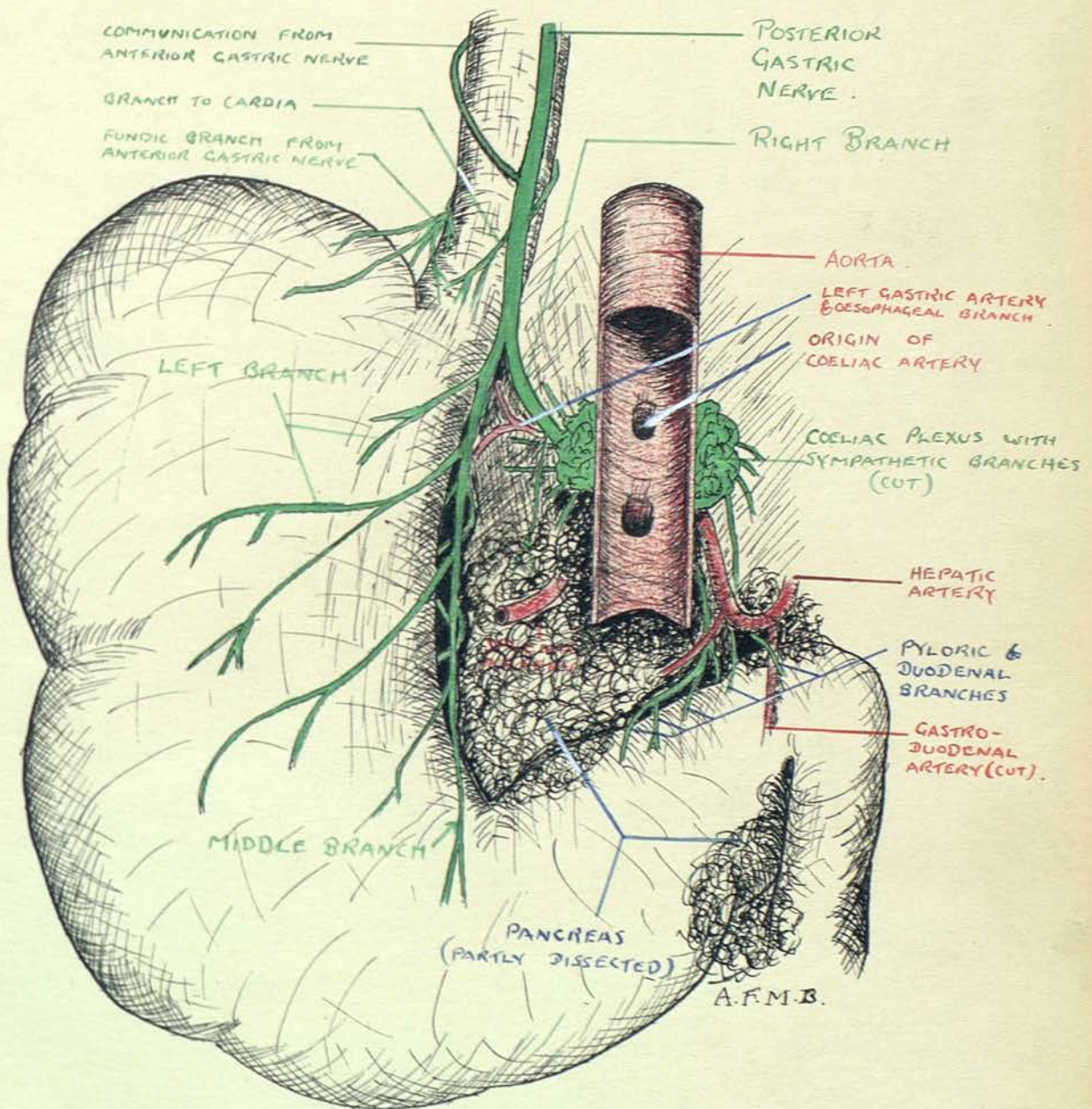
numerous sympathetic nerves emerging from the coeliac network run alongside the hepatic artery in a retrograde manner, then pass with the gastroduodenal artery, to end in the pylorus, pyloric canal and 1st part of the duodenum.

(b) The Middle Branch corresponds to the similar one from the Anterior Gastric Nerve. It runs along the lesser curvature giving branches to adjacent parts of stomach and communicating by a few very fine fibres with the Middle branch of the Anterior Nerve. It also ends near the Incisura angularis.

(c) The Left Branch is a smaller nerve than its anterior companion and is distributed to the posterior surface of the Body of the Stomach.

(Fig. 2)

FIGURE 2.



A SKETCH FROM A DISSECTION TO
SHOW THE BRANCHES OF POSTERIOR
GASTRIC NERVE (O.T. RIGHT VAGUS).

THE SYMPATHETIC NERVES.

The highest centre is in the posterior part of the Hypothalamus behind the tuber cinereum and separated from the vagal centre by a "silent" area(16) (17). Fibres may arise from this centre and travel in the substance of the brain and cord to the Inter-medio-lateral Grey Column but it probably carries out its actions through the liberation of hormonal substances which act at a distance.(20) The secondary centres, however, are in the Intermedio-lateral Grey Column of the Thoracic part of the Spinal Cord. Axons pass out in the white rami communicantes, pass along the Sympathetic Trunk and emerge as the Splanchnic Nerves which end in the Coeliac Ganglion (21). Sympathetic fibres after relaying in that ganglion stream out in two directions - along with the left gastric artery, and with the hepatic and gastroduodenal arteries and their branches. In their course near the stomach they run parallel with vagal bundles. (Fig. 3)

FIGURE 3.

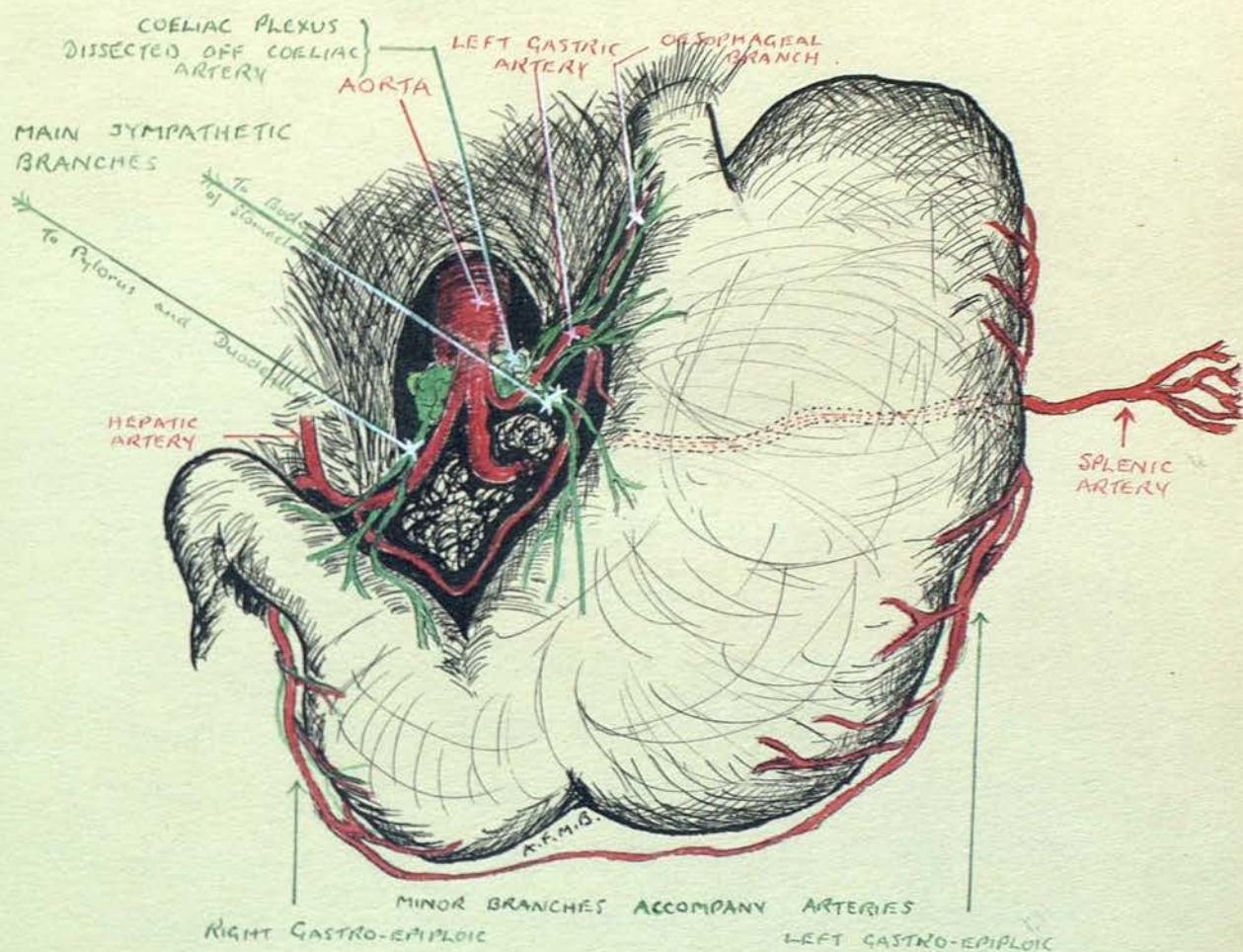


DIAGRAM TO ILLUSTRATE THE
DISTRIBUTION OF SYMPATHETIC
NERVES TO THE STOMACH.

INTRINSIC NERVOUS SYSTEM.

This consists mainly of 2 plexuses viz. the Myenteric plexus, situated between the longitudinal and circular muscle coats, and the Submucous plexus situated in the submucosa. They are just parts of the Enteric Plexuses which extend from the upper levels of the oesophagus to the anal canal.

The plexuses are composed of innumerable small ganglia interconnecting with each other and with the extrinsic nerves. It is here that the (post ganglionic) parasympathetic fibres end, arborizing around ganglion cells. Sympathetic ^(post-ganglionic) fibres take part in the plexus but not in any synapses. Their functional activity is not abolished by section of the nerves through which they are connected to the central nervous system, and this seems to indicate as experimental work has shown, that they form local reflex mechanisms. (22)

Keith describes special nodal tissue and conduction paths leading down the lesser curvature which he thinks regulate the peculiar peristalsis and automatic motility of the stomach.

Klein accepts this as an explanation for the disorders of motility so frequent in gastric ulcers and after wedge resections of such ulcers. He points out/

out that the stomach is divided functionally into bands of muscle passing circularly round the organ. An ulcer of the lesser curvature is so frequently associated with a ring of contraction right round the stomach giving an hour-glass effect radiologically.

(22) (23) (24) (25) (26) (27) (28) (29) (30)

V. THE PHYSIOLOGY OF THE STOMACH AND
 ITS NERVES.

(1) THE LOCAL PHYSIOLOGY OF STOMACH AND DUODENUM.

(Only a very short summary is given under this head, as true perspective can only be attained after the results of recent experimental work, discussed later, have been considered.)

Functionally the stomach may be divided into 3 regions.(31) (Fig. 4)

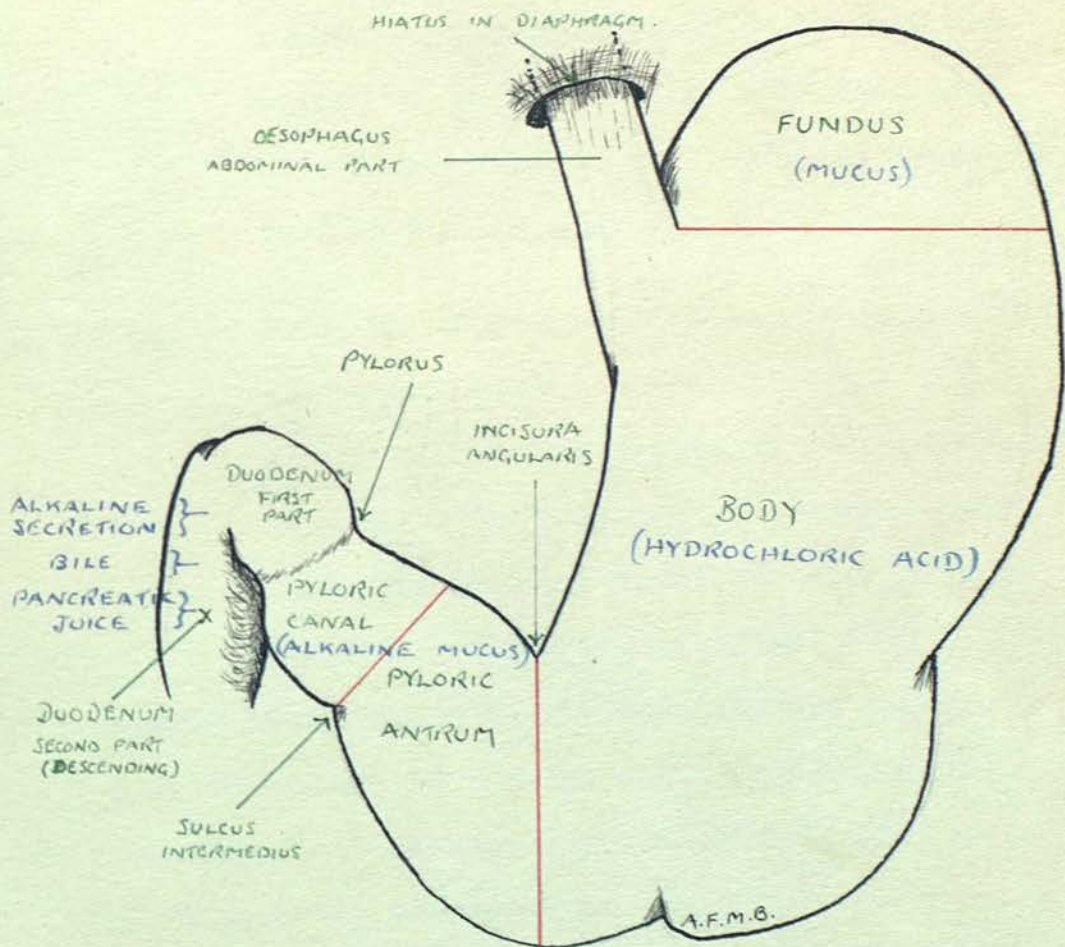
Fundus: - i.e. the part above the cardiac orifice.
 Its glands secrete mainly mucus and a
 little pepsin.

Body: - from cardia to a point just beyond the
 incisura. Its glands secrete hydro-
 chloric acid, pepsin and mucus.

Pyloric Part (Pyloric Canal and Antrum): - from
 end of body to Pylorus. Its glands
 secrete slightly alkaline mucus.

Pylorus: - does not act as other sphincters in the
 body by alternatively either giving free
 passage or blocking the flow of contents
 of the viscus above, but maintains a
 considerable degree of tonus the whole
 time/

FIGURE 4.



TO ILLUSTRATE THE ANATOMICAL
AND FUNCTIONAL DIVISIONS OF
THE STOMACH

time acting somewhat after the manner of a sieve, allowing fluids and finely divided particles to pass and, according to conditions operative, allowing stomach contents into the duodenum, or duodenal contents into the stomach. In fact the action of the pylorus is well described by a translation of the original Greek *πυλῶρος* , a gate keeper.

Duodenum. Contents consist of pancreatic (external) secretion, bile, secretion of its own glands and some contents of stomach and jejunum. The reaction of duodenal contents uncontaminated by stomach juice is neutral or slightly alkaline. (32)

The stomach with regard to its motility and secretion is, like the heart, to a large extent automatic in its functions and apparently operates well for some time when entirely removed from the body. (33)

Its functions however are to an extent regulated by its extrinsic nerves and chemical or hormonal substances delivered through its blood vessels. It would appear that lesions of these extrinsic controlling systems are responsible for diseases of the stomach.

Vagal stimulation alters the existant conditions in/

in the stomach in the direction of hypermotility, hypersecretion and hyperchlorhydria, whereas sympathetic stimulation results in changes in the direction of atony and secretion of mucus.

Chemical substances of the nature of Adrenalin and Acetyl Choline probably elaborated away from the stomach may produce similar results.

(2) THE PHYSIOLOGY OF THE AUTONOMIC NERVOUS SYSTEM.

The main points in connection with the Autonomic Nervous System are well known and need not be repeated. There are one or two aspects however, which must be particularly remembered if the rationale of the experiments described hereafter is to be understood.

1. The controlling centre for the whole Autonomic System it has recently been shown is in the Hypothalamus and it is divided into 3 parts. Anterior (or supraorbital), Middle and Posterior. Stimulation of the anterior part gives a pure Parasympathetic (vagal or cholinergic) action: the middle part is 'silent' while stimulation of the Posterior part results in pure Sympathetic or Adrenalgic response. There are secondary centres in the medulla on the floor of the 4th ventricle.

The hypothalamic centres are in close proximity to the centres for the emotions in the thalamus and are directly under the higher centres in the cerebral cortex. Hence upsets in the higher centres or in the emotions have not far to go to reach the "heart" of the Autonomic system. (16) (17)

2. The path of autonomic impulses from centre to viscus is not a continuous one. There are synapses in or near the viscus to be supplied and the final action is brought about by the parasympathetic nerve endings/

endings elaborating acetyl choline which gives the result we know to accrue from vagal stimulation. Similarly sympathetic nerve endings produce adrenalin. Hence Sir Henry Dale has suggested that better names for parasympathetic and sympathetic nerves would be Cholinergic and Adrenalergic respectively and this is being gradually adopted. (34) Drugs similar in their action to these two therefore produce actions in the body similar to those obtained by actual nervous stimulation.

3. Overaction of one of the Autonomic Components may be absolute or relative. Thus stimulation of the vagus to a viscus gives an absolute vagal overaction, but paralysis of the sympathetic produces very similar, though probably not identical, results by removing the action of the one component (sympathetic) and allowing relative vagal overaction to ensue. Similarly, cutting the vagal supply to a viscus closely imitates stimulation of the sympathetic.

4. The peripheral vagus is not 100% cholinergic but contains a few (greatly in the minority) adrenal-ergic or sympathetic fibres. The sympathetic nerves so called are similarly not 100% adrenalergic. This fact probably explains why occasionally one gets results directly opposite from expectations. (19)
(35) (36) (37) (38)

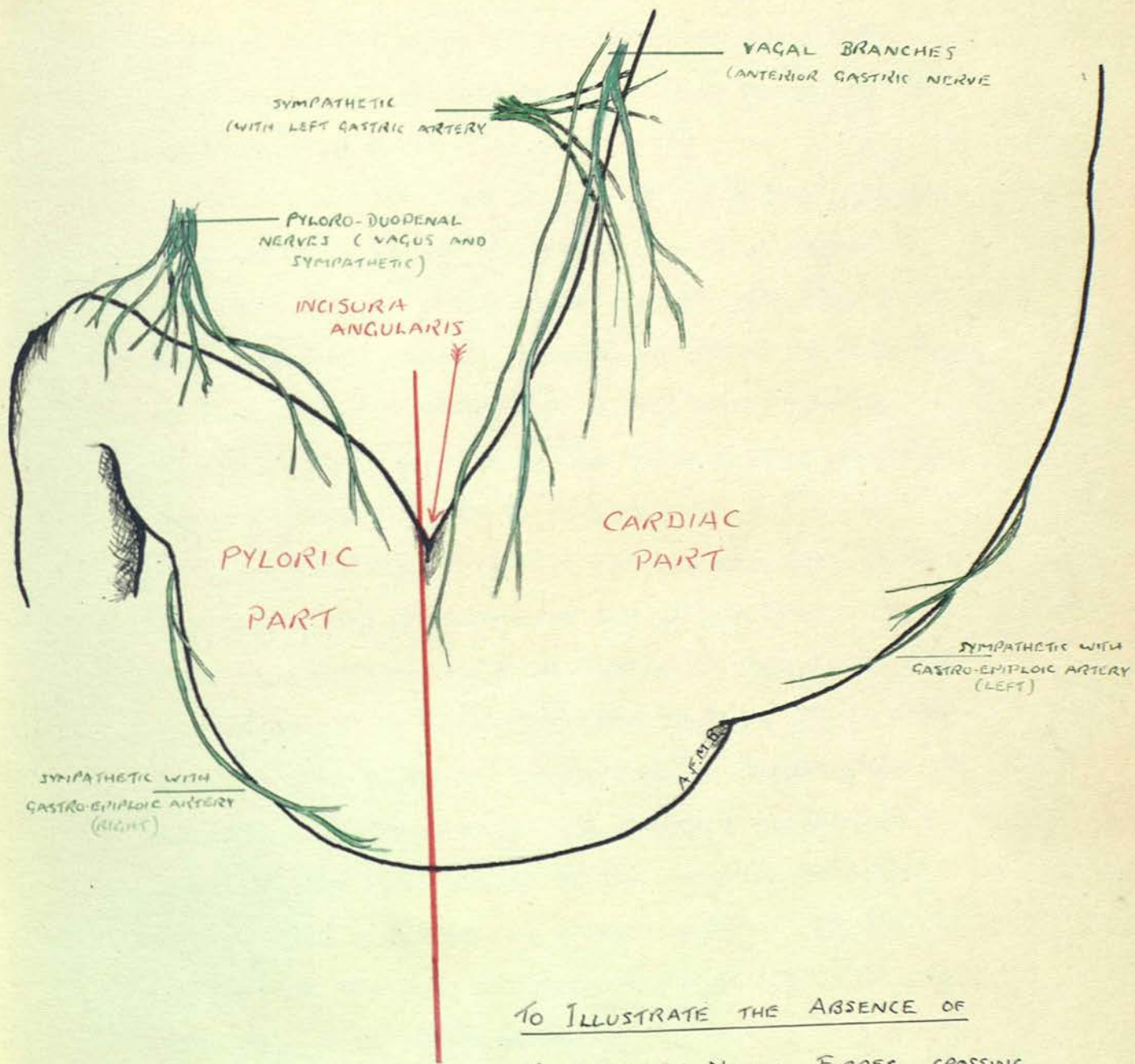
(3) SPECIAL POINTS TO NOTE IN THE ANATOMY AND
PHYSIOLOGY OF THE STOMACH.

Several facts emerge from these dissections which are not generally recognised by most surgeons. Probably the most striking one is the entire absence of extrinsic macroscopic nerve fibres passing between the incisura angularis and the pylorus. (See Fig. 5)

The direct branches of both gastric nerves stop near incisura as do the sympathetic fibres following the left gastric artery. The pylorus gets its nerve supply from above; sympathetic from coeliac plexus, vagus almost entirely through Right (or Hepatic) Branch of anterior gastric nerve, the pyloric branches of which descend from the Porta Hepatis.

This may explain the disappointing results which have followed nerve section operations (a few of which have been done in Edinburgh and elsewhere) at the middle of the lesser curvature, in cases with functional pyloric stenosis (pylorospasm) and hyperchlorhydria, with the idea of cutting the nerve supply to the pylorus and so abolishing spasm. (39) It also may explain the observation (40) that cases of gastric ulcer situated either high up on the lesser curvature or close to the pylorus usually do well with simple gastro-enterostomy whereas in ulcers situated/

FIGURE 5.



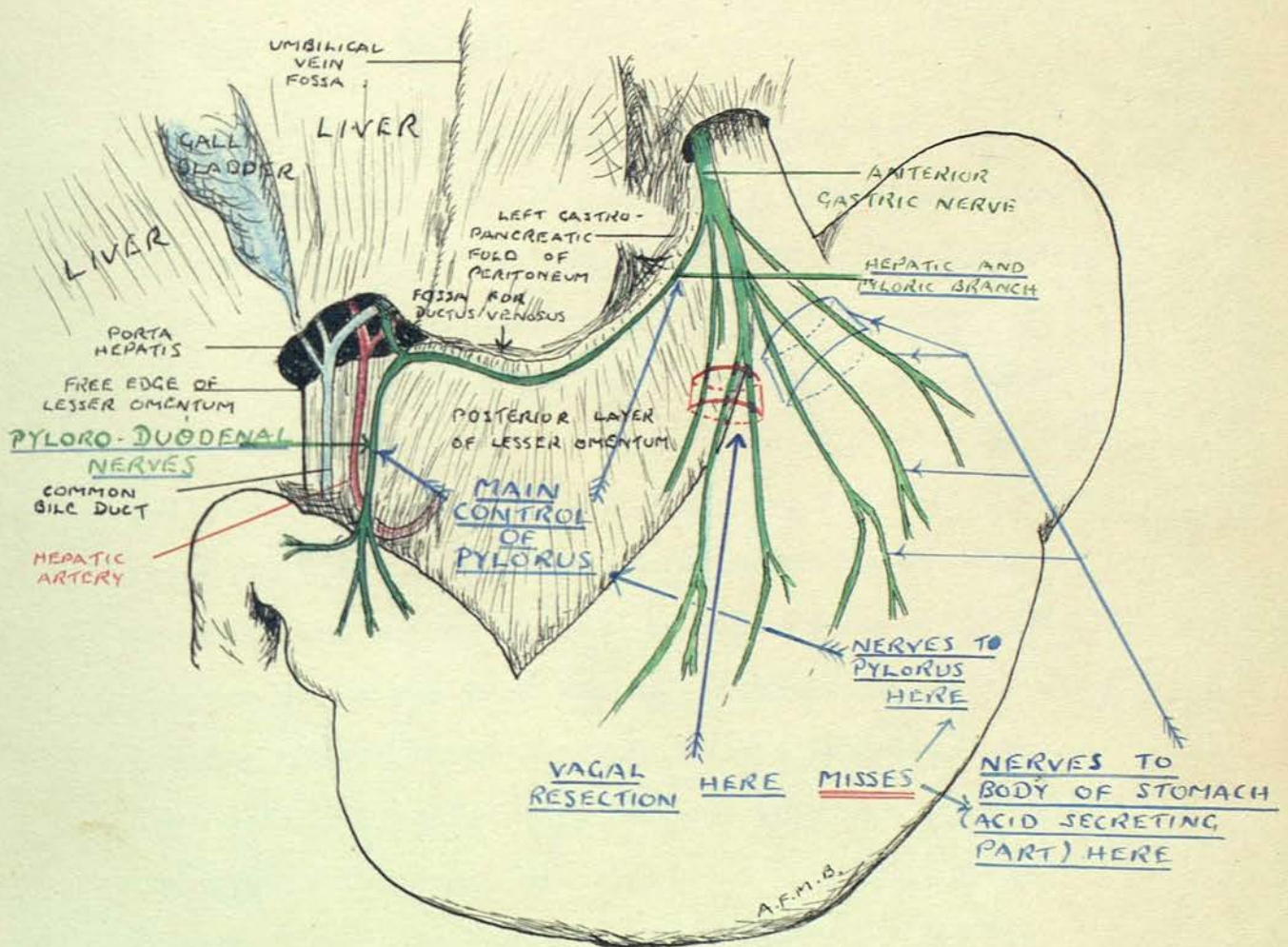
TO ILLUSTRATE THE ABSENCE OF
MACROSCOPIC NERVE FIBRES CROSSING
BETWEEN CARDIAC AND PYLORIC PARTS
OF THE STOMACH.

situated in the mid-part of the lesser curvature symptomatic relief obtained from that operation is not nearly so great.

The reaction from ulcers in the former situation presumably irritates the right branch of anterior gastric nerve directly in its course (See Fig. 6 at points marked) causing pylorospasm which is indirectly or functionally relieved by anastomosis, whereas ulcers in the latter site owe their main symptoms to other factors not due to pylorospasm.

A consideration of the anatomy may also explain why operations of nerve section on the lesser curvature have failed to relieve hyperchlorhydria unless the resection of the structures on the lesser curvature is done right at the cardia, or a subserous resection is carried on on the anterior surface of the stomach, the Left Branch of the Anterior gastric nerve which supplies the greater part of the anterior surface of the body of the stomach escapes altogether (See Fig. 6 at point marked).

FIGURE 6.



To Illustrate the Paths of Nervous
Control of Pylorus and Acid Secretion.
Common Errors in Vagal Neurectomy
Operations are also indicated.

VI. THE IMMEDIATE CAUSES AND CONCOMITANTS OF GASTRIC AND DUODENAL ULCERATION.

1. THE ACID FACTOR.

It may be stated without fear of contradiction that the main single factor associated with the production of "peptic" ulceration is the hydrochloric acid as elaborated in the gastric juice.

Brief consideration will immediately bring many facts associating ulcer with hydrochloric acid to mind. One of the first is the occurrence of "peptic" ulceration only in those sites where hydrochloric acid abounds; and no region open to the action of hydrochloric is immune from typical chronic ulceration i.e. bearing ulcers which may last weeks, months or years, have slightly rolled margins, eat into the walls of the viscus affected, are liable to perforate right through them; their surface is frequently infected, gastritis or duodenitis may be observed in the surrounding mucosa; microscopically the ulcers are encircled by reactionary fibrous tissue, and thrombosis of some of the smaller vessels is frequently observed.

Typical "peptic" ulceration, then, occurs only in:-

The Lower End of the Oesophagus - Hydrochloric

Acid being present as the secretion of aberrant gastric glands, or regurgitation from the stomach; the Stomach, especially the Lesser Curvature;

The First Part of the Duodenum;

The Jejunum, only after gastro-enterostomy and
near the stroma;

The Ileum, only in those cases where a Meckel's
diverticulum with aberrant gastric mucosa
is present.

In all the above sites it will be noticed Hydrochloric
Acid is present, in a concentration nearing the max-
imum secreted by oxyntic cells. (41) (42)

The uncontrovertible importance of hydrochloric acid
is well shown in the researches of Dragstedt of
Chicago, and I could do no better than give some
extracts from recent reports:

"All living tissues will succumb to the digestant
action of the gastric juice, where conditions are such
that they are exposed to the pure undiluted secretion,
provides further support to the theory of the "peptic"
genesis of ulcer. Whereas it was found that organs
such as the spleen and kidney, when implanted into
the wall of the normal stomach and consequently ex-
posed to the usual gastric content remained little
affected, they were promptly digested away when they
were implanted into the wall of an isolated stomach
pouch and exposed to the action of pure undiluted
gastric juice. In a somewhat similar type of experi-
ment it was demonstrated that the pure fundus (in
English terminology i.e. body) secretion can digest
away/

away the normal mucosa of the alimentary tract including that of the stomach itself, the resulting defect displaying all the gross and histological features of chronic progressive ulcer in man. Under normal conditions the gastric juice is diluted and partly neutralized by swallowed food and saliva, the secretion of mucus, and to a certain extent by the regurgitation of bile and pancreatic juice."

And later he goes on to say:-

"A very important remaining problem is to outline those factors which lead to the accumulation in the stomach of a content that resembles pure gastric juice in acid and enzyme concentration. Pyloric stenosis with retention and excessive "continuous secretion" are two conditions which come readily to mind The mechanism of the "continuous secretion" of gastric juice is little understood and the factors that alter its volume are unknown. There is evidence that this secretion is excessive in many ulcer patients, and is perhaps "nervous" rather than "humoral" in origin.

Of the two elements, pepsin and Hydrochloric Acid in gastric juice, it is the concentration of the acid that determines the ability of the secretion to digest living tissue. When the legs of living frogs were exposed to the digestant action of gastric juice samples of varying acid and enzyme concentrations/

concentrations being taken, the extent of digestion varied as concentration of acid and little if at all with the pepsin.

Approximately 0.15% free Hydrochloric Acid was the critical level below which the living tissue was not affected. When the acidity of the juice exceeded this level the exposed living tissue was digested away although the pepsin concentration had been reduced to one-tenth of its original value. It is doubtless significant that the free acidity of the normal gastric contents of man rarely exceeds 0.15% (42 clinical units) and that higher values are commonly found in ulcer patients. The relatively greater importance of the acid in the genesis of ulcer is further suggested by certain observations made with pancreatic juice. Trypsin is more active than pepsin but no tryptic ulcers of the duodenum in the region of the pancreatic ducts have been described. Furthermore the legs of living frogs exposed to pure activated pancreatic juice were not digested away as was the case with gastric juice. Accordingly if it seems wise to stress the importance of the chemical action of the gastric contents in the aetiology of Gastric Ulcer and Duodenal Ulcer, the term "acid ulcer" is more accurate than "peptic" ulcer and serves to direct attention to the more important element in gastric juice." (43) (44) (45) (46) (47)

Numerous/

Numerous workers have injured the mucosa of the stomach of experimental animals and then introduced at regular and frequent intervals by tube or fistula, Hydrochloric Acid of varying concentrations in the hope of making the acute traumatic lesion into a chronic one. Although healing has been delayed with Hydrochloric Acid of pH 0.9 concentration or stronger, chronic lesions have not been produced. (48) This failure is illustrative of the efficiency of the defensive power of the stomach against noxious materials.

The two great factors operating against deleterious agents and indeed preventing the stomach from being digested by its own products are Dilution and Neutralization, the Dilution by food and regurgitation of duodenal contents, Neutralization by the mucus secreted by the stomach and to a lesser extent by some Alkaline foods.

For many years the Boldyreff Theory of duodenal regurgitation occurring whenever the gastric contents reached a certain degree of acidity, the duodenal juices and contents then neutralising the gastric content, held sway, and is still adhered to by many of the less progressive clinicians. (49)

It has been shown time and again however, that weaker acid (e.g. 0.2% Hydrochloric Acid) introduced into the stomach frequently produces more marked regurgitation/

regurgitation than do stronger acids (e.g. 0.5% Hydrochloric acid); that ingestion of alkalis (e.g. 1% to 5% Sodium Bicarbonate) often produces greater amounts of regurgitation than either the aforementioned acids even though the gastric contents remain alkaline or neutral throughout the test period; and that great quantities of regurgitation take place in cases of achylia gastrica. Moreover the duodenal contents are only very slightly alkaline and no duodenum, liver and pancreas yet created could possibly cope with even an inferior acid producing stomach. (32)

It used to be thought that the stomach had some inherent power of controlling the acidity of its contents, but this has been disproved by more recent experiments. The stomach has no power of regulating the acidity of the gastric juice either by its final transformation into a neutral solution or by the addition of pyloric juice which appears to play no greater part in this respect than the mucous secretion of the body of the stomach. When any substantial reduction of acidity occurs the percentage of total chloride falls, showing neutralisation and dilution by mucin and not replacement of acid by neutral chloride. Gastric secretion continues with undiminished acidity although it is allowed to accumulate in the stomach in a dog whose pylorus has been occluded.

The/

The contention that the presence of a certain concentration in the stomach inhibits further secretion of acid is thus erroneous. (50) (51) (52) (53)

Mucus appears to form the most successful control of acidity, and apparently controls it completely in the normal resting stomach. The mucus is a protein and in the presence of pepsin probably combines with the acid to give an acid mucin and a neutral chloride. The neutralization certainly cannot be accounted for on the basis of a reaction between an acid and an alkali, because of the weakly alkaline character of the mucus. It is probably dependent on a protein - acid combining phenomenon as suggested by Foster's (1907) experiments. (54) (53)

The Neutralization and Dilution effect of various foods is well illustrated in the success of the Sippy Treatment and its modifications in hyperacidity and can be seen in studying almost any chart of a clinical 'Fractional Test Meal' (Rehfuss). (See Fig. 7)

Wylie working for an M.D. Edin. Thesis has shown by means of extended fractional test meals how very good milk is in reducing acidity. (55)

I, myself, in incidental experiments on cats (the method to be described later in this thesis - pages 118) ^{et seq.} have shown the power of milk in this direction/

GASTRO-INTESTINAL ANALYSIS.

Name of Patient MARY C. Ward 25 Bed

I. FRACTIONAL TEST-MEAL. Date.

Fasting Juice.Volume. 12 cc.

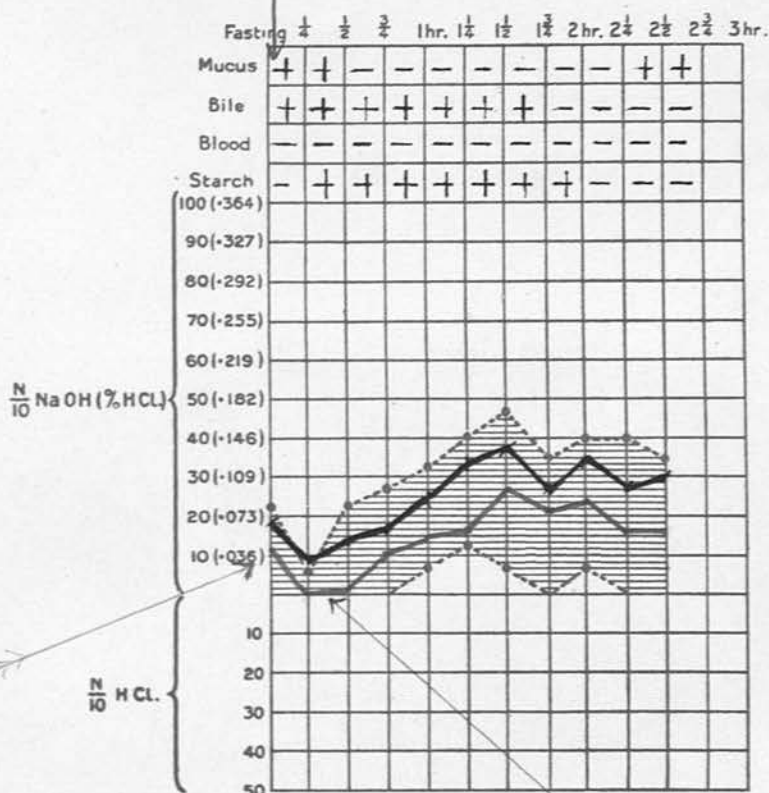
Cells.

One Hour Fraction.

Free HCl.

Active HCl.

Total Chloride.



The shaded area represents the limits for free HCl. in 80% of normal people, and average rate of emptying (2-2½ hours).

RED represents free HCl.
BLACK represents total acidity.

ACID DILUTED AND
 NEUTRALIZED BY FOOD.

Summary.

NORMAL ACID CURVES. NEUTRALISATION
AND DILUTION OF ACID BY FOOD IS SEEN.

2. FÆCES.

direction. Fig. 8 shows test meal charts of cats starved for 24 hours and then given (1) Fish, (2) Fish and Milk, the total meals in (1) and (2) being of approximately equal weight.

The animal appeared equally hungry in each case and ate the fish and lapped the milk with equal gusto, so that the main (psychic) secretion was probably produced by stimuli of similar intensity. (See Fig. 8) But however efficient and automatic these safeguards against hyperacidity may be in the majority of cases, in some they prove disastrously inadequate. It has been known since the early work of Pavlov that the stomach can react and maintain a high rate of secretion. This has been checked and expanded by recent workers and it emerges that during the course of gastric digestion the Hydrochloric Acid is secreted at a constant level of 0.5%, a normality of 0.135 or a pH of 0.87 with full ionisation. (56)

There is evidence also that a high rate of secretion in some people is maintained long after the meal is over, or indeed independently of food altogether and that this "excessive continuous secretion" arises from nervous stimulation through the vagi. No neutralizing mechanism in the body can reduce to normal levels this huge acidity which therefore can carry out its felonious work unchecked.

Before/

GASTRO-INTESTINAL ANALYSIS.

Name of Patient

CAT 5

Ward

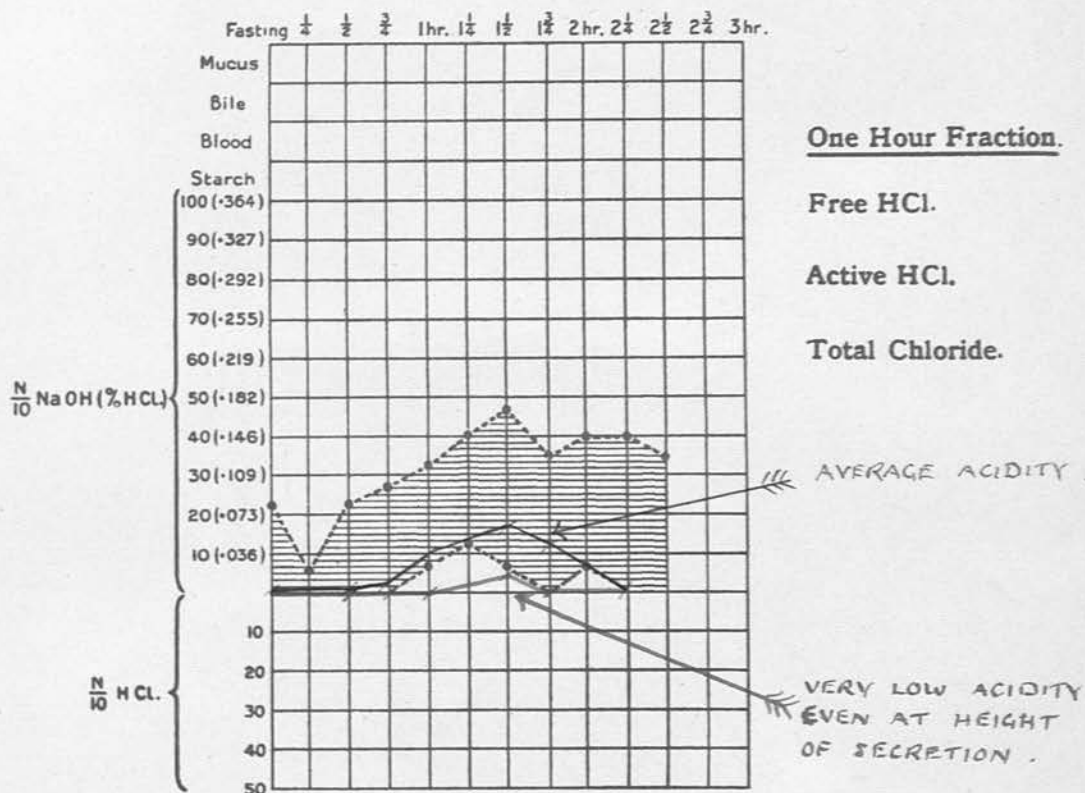
Bed

1. FRACTIONAL TEST-MEAL. Date.

Fasting Juice.

Volume. 1 cc.

Cells.



The shaded area represents the limits for free HCl. in 80% of normal people, and average rate of emptying (2-2½ hours).

GREEN represents free HCl. WITH FISH TEST MEAL.
 RED represents total acidity. WITH MILK TEST MEAL.

Summary.

MILK IS A VERY EFFICIENT NEUTRALIZING
 AGENT FOR GASTRIC ACID.

2. FÆCES.

Before we leave this subject of the local chemical control of gastric acidity to deal with the more remote and nervous control in the next chapter, there is one question which springs to the mind.

In the last few pages the Hydrochloric Acid has been put down as being a pre-ulcerous factor. Might not an awkward question of precedence similar to the age old one of the hen and the egg be involved?

In this case the question is easily answered however. It is not an uncommon occurrence, and I have noted it personally on several occasions during my tenure of House Physician and House Surgeon posts in hospital, that a patient is known to have a considerable hyperchlorhydria and yet repeated examinations by a competent radiologist have revealed no ulcer, yet some months or years later that same patient has returned and is found to have the same degree of hyperchlorhydria or even a little less but an obvious duodenal or gastric ulcer by X-rays.

On the experimental side, if the Mann-Williamson operation is performed on dogs (57) and in addition a jejunal fistula is made immediately distal to the gastro-jejunal stoma, it can be shown that the reaction of the jejunal contents in the area where the ulcer forms, have the same pH before and after the formation of an ulcer. These findings, I think are a sufficient answer to the question. (58)

Although it is a most intriguing fact that regurgitation of duodenal contents into the stomach appears to be a normal part of the digestive processes, it is not quite the truth to say that disorders of this mechanism are the one cause of gastric and duodenal ulceration. Yet so firm a hold had the Boldyreff theory of Duodenal Regurgitation obtained on the minds of most medical men that for many years some abnormality in the duodenal contents or in the direction of their flow was looked on as the sole probable cause of "peptic" ulceration. And a great many structures were blamed for the abnormality. If it was not the liver that was producing inferior bile then it was the gall-bladder that was adulterating it; if it was not the pancreas that was having an attack of dysfunction, then the sphincter of Oddi was not behaving itself. Of course the arch-offender implicated by nearly all was the Pylorus which appeared to take spontaneous spasms or convulsions at the most unwelcome moments. Indeed the number of indicted structures was only equalled by the prodigality of ingenuity shown by investigators in devising experimental operations for "proving" the innocence or guilt of their particular fancy. Thus operations from well nigh complete hepatectomy, to the establishment of a one way traffic system for the duodenum, by the introduction/

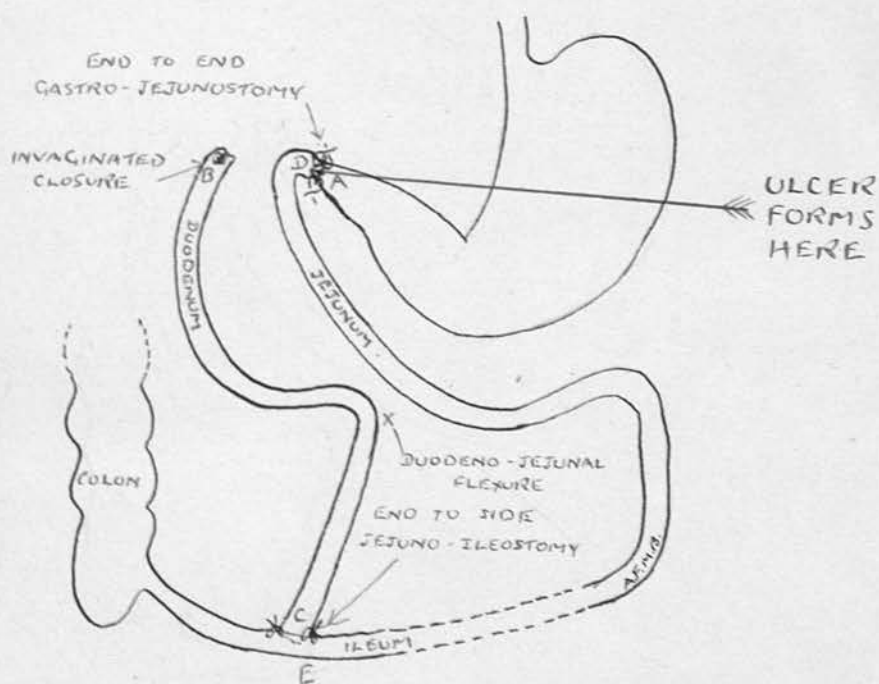
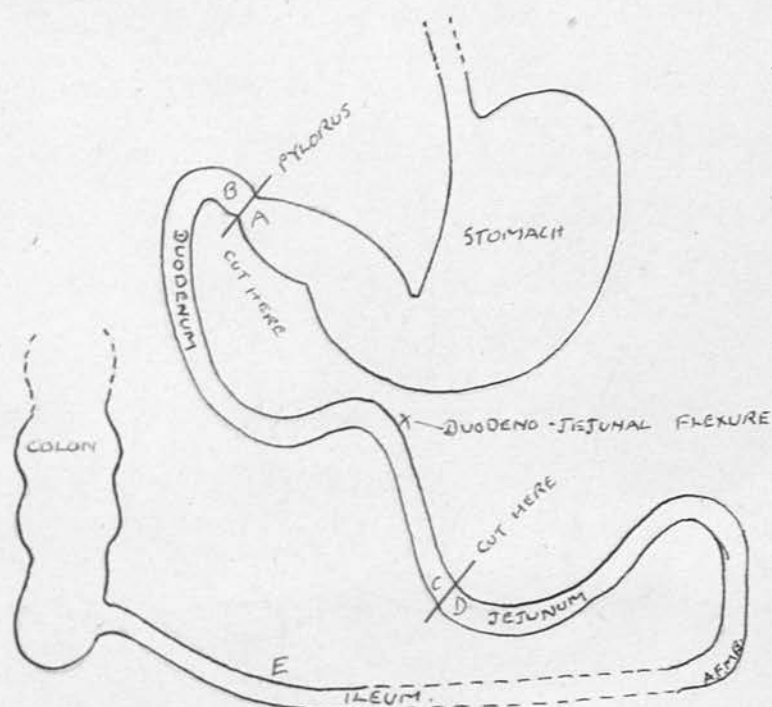
introduction of special valves into various parts of the alimentary tract were tried.

In some of the less fantastic operations, the bile and/or pancreatic ducts have been transplanted either externally or into the lower ileum or colon and a gastro-jejunostomy also performed. In the dogs surviving this severe procedure, a considerable number have developed an indurated ulcer in the jejunum just beyond, or impinging on the suture line of the anastomosis. (59) (60)

The standard operation of this type however, was introduced by Mann and Williamson in 1923 and is termed Internal Duodenal Drainage (57). Its effect is functionally to remove the duodenal (including bile and pancreatic) secretions from the possibility of entering the stomach yet to prevent their usual digestive effects being entirely lost to the small intestine.

The dog is the animal used and the stomach severed from the duodenum by incising right through the gut at the pylorus and turning in the ends. The continuity of the jejunum as near the duodeno-jejunal juncture as possible is also dissolved and the open distal limb of the jejunum anastomosed to the stomach either at the place where the pylorus was (end to end gastro-jejunostomy) or through a new incision near there/

FIGURE 9.



A DIAGRAMATIC REPRESENTATION OF THE
MANN / WILLIAMSON OPERATION FOR THE
PRODUCTION OF CHRONIC "PEPTIC" ULCERATION.

there. The duodenum and a small piece of jejunum is now quite unconnected with the re-established gastrointestinal canal. The upper end of the duodenum is already closed, and the small proximal limb of jejunum is anastomosed with the side of the distal ileum 25 to 75 centimetres from the caecum (end to side jejuno-ileostomy). With an expert operator the mortality is stated to be quite low, and the dogs remain in good condition. Often, in the 3rd or 4th week after operation, a sudden loss of weight occurs and this is associated with the formation of an ulcer in the jejunum close to the gastro-jejunal stoma. Such ulcers form in about 75% of cases and show all the criteria of chronicity - induration, infiltration and special liability to perforate, etc.

The deductions made from these experiments are that the ulcer is caused by the action of the gastric juice acting on the jejunal mucosa which has no "natural protection" against it as the stomach has. The principal assumption is, however, that the duodenal contents (especially the bile) neutralise the gastric juice and also contain some special protective substance or anti-ulcerative principle.

That the bile should normally neutralise the gastric acid is inconceivable as has already been shown; but it may dilute it to such an extent that it/

it comes below the mucosal digestive threshold, because it must be remembered that large quantities of bile are normally secreted - 500 to 1000 cc. in 24 hours, of which, of course a considerable quantity is concentrated in the gall-bladder before release into the duodenum. (61) An added post-operative factor also, is the ability of all kinds of food unsuitable in both temperature and consistence to come quickly into contact with the jejunal mucosa, through the stoma, which is designed only to receive food suitably "milled" and partially digested in stomach and duodenum.

Although the experiment is a valuable one in studying certain aspects of chronic ulceration, its use in so far as throwing light on the aetiology of chronic gastric and duodenal ulcer in man is rather questionable on account of the severity of the operation and the great alteration in the normal continuity of the alimentary tract. The ulcers also are jejunal not gastric or duodenal, although that fact may not be so important as it would appear at first sight.

(2) MECHANICAL FACTORS.

It is a well known fact in the mechanics of the stomach that substances coming down the oesophagus tend to be shepherded along the lesser curvature to the pyloric canal - the so-called Magenstrasse - rather than to be allowed to fill up the lumen of the whole viscus at random. It is therefore evident that the magenstrasse bears the brunt of any abrasive or otherwise irritant food, so much of which finds a prominent part in the average man's diet to-day. It is also a fact that it is precisely in the area of that tract that the overwhelming majority of chronic ulcers of the stomach are situated.

Connected with these findings may be the large incidence of chronic "peptic" ulcer in Holland - about twice as great as in this country. In Holland it is held that the average diet is much more irritating than in Britain, containing as it does a high proportion of virulent seasoning agents and coarse vegetables. The men there also drink more spirits and smoke more, often swallowing the acrid juices. (62)

The first part of the duodenum may possibly receive recurrent traumata, too, because it is a well-known/

well-known finding, seen radiologically, that active stomach peristalsis combined with slight relaxation of the pylorus frequently squirts highly acid contents against the duodenal "cap" with considerable force as from a hose nozzle. In this may the old proverb find its illustration - "constant dropping wears the stone".

The place of gastritis in production of ulcer is difficult to assess. That it is a very frequent accompaniment is not now doubted but whether it occupies the position of cause or effect is a moot point. Much useful information has been gained from examination of specimens from the carnivorous operations of Konjetzny, and with the improvements in gastroscopy which are now going on apace, a clearer outlook may be expected in the near future. (63) (64) (65)

VII. THE MORE REMOTE CAUSES AND CONCOMITANTS
OF ULCERATION.

1. THE EXTRINSIC FACTORS IN THE CONTROL OF
GASTRIC ACIDITY.

The broad outlines of the local physiology of gastric secretion have been studied since 1825 (Beaumont), till the culmination was reached in the work of Pavlov. They are well known and in the main need not be repeated here. There are however, many points relating to the means of stimulating gastric secretion and to the paths through which control of digestion is maintained, which must be discussed before pathological abnormalities can be usefully considered. The Secretion of Gastric Juice may be divided into 4 phases: Psychic, Reflex, Gastric, and Duodenal or Jejunal.

1. Psychic juice appears in the stomach shortly after an hungry animal has been allowed to see or smell food, or in fact after any stimulus which the animal connects with food has been allowed to impinge on the special senses.
2. Reflex juice appears in the stomach shortly after food has been taken into the mouth, as was shown in "sham feeding" experiments in dogs with oesophageal fistulae where the food was eaten/

eaten by the dog but slipped out of the fistula without getting to the stomach.

3. Gastric phase of secretion occurs from one to four hours after food has entered the stomach and is initiated by the presence of particular foods in the stomach.
4. Duodenal and Jejunal phases are similar to the third phase and depend for their stimulation on the presence of particular foods in duodenum or upper jejunum.

The relative importance of the part played by the above means of stimulation can be well seen on studying the results of one of Pavlov's experiments (only one of many similar in technique and results) stated diagrammatically in Fig. 10.

FIG. 10./

FIG. 10.

HOURS	NORMAL MEAL.		MEAL INTRODUCED DIRECTLY INTO STOMACH		SHAM MEAL.		SUM OF LAST TWO EXPERIMENTS.
	Quantity c.c.	Strength m.m.	Quantity c.c.	Strength m.m.	Quantity c.c.	Strength m.m.	
1	12.4	5.43	5.0	2.5	7.7	6.4	12.7
2	13.5	3.63	7.8	2.75	4.5	5.3	12.3
3	7.5	3.5	6.4	3.75	0.6	5.75	7.0
4	4.2	3.12	5.0	3.75	0	0	5.0

The animals used were dogs prepared with oesophageal and gastric fistulae. On two separate occasions a dog was given a sham meal and a similar meal introduced directly into the stomach, care being taken not to excite the Psychic mechanism.

Thus on the former occasion, juice produced by psychic reflex stimulation was obtained and measured while on the latter that from the gastric and intestinal phases was estimated. The result of a normal meal on a dog with a gastric diverticulum is also given. The normal meal was 200 gms. of meat and the two test meals were 150 gms. of meat. The digestive strength of the juice was determined by measuring the number of millimetres of coagulated egg white (in Mett's tubes) which were digested in eight hours.

It will readily be seen that the psychic and reflex juice is by far the most potent and also that when the 2 experimental test meal results are added together they correspond closely to the result of a "normal" meal.

(a) Nervous Control of Gastric Acidity.

What was even more interesting to me in composing this thesis was the fact, which has been proved beyond any possible doubt, that bilateral section of the vagi absolutely abolishes the psychic secretion. Sympathetic section has no effect in this direction.

Much experimental work has been done on the action of the vagus in relation to gastric secretion at McGill University, Toronto. It is suggested on experimental basis that the vagus quite probably not only causes the secretion of gastric juice but has a differential secretory function on the various contents of that juice, differing stimuli secreting Hydrochloric Acid, pepsin and mucus in varying proportions. (42)

It has also been shown that when gastric secretion was excited for several hours by repeated injections of histamine (the most powerful chemical excitant of gastric secretion known), the pepsin content of the juice soon fell to zero, while the acid continued. Prolonged vagal stimulation however, gave a juice rich in both acid and pepsin, of great digestive potency, and moreover also caused the reappearance of pepsin in the juice after it had apparently been exhausted by continuous injection of histamine.

The acidity of the gastric juice thus induced was constant, or nearly so, at about 0.5% Hydrochloric acid during the height of secretion. At the beginning and the end, the juice is mixed with mucus which dilutes and neutralises the acid. (See Page 36)

From these "acute" experiments then, one can visualise the possibility that due to some abnormality in the Autonomic Nervous mechanism, an adequate stimulus/

stimulus for vagal secretion may exist in certain cases quite apart from the presence of food. In which case, gastric juice of high digestive potency would be in contact with the stomach and duodenal wall, there being no food in these viscera to deviate it. Animal experiments suggested by the above possibility have been evolved by the author and will be described in a later chapter.

Quite apart from its secretory function, the vagus nerve has others which have been recognised since the earliest days of modern psychology. It is the motor nerve to the Alimentary Tract. A huge volume of work has been done literally by hundreds of workers on this aspect of vagal function, and no attempt will be made to report all the various findings contradictory and otherwise. By sifting the varying results and discarding those experiments containing obviously faulty technique we arrive at the conclusion that the vagus is not a motor nerve in the usual sense of the word. The action it has depends largely on the state of "tonus" in which the stomach is at the time of stimulation, and may be inhibitor or augmentor; but whatever the initial effect of stimulation is, the ultimate one is to bring about the augmentation of existing movement or to initiate movement. (66)

In practice, stimulation of vagal fibres in one way/

way or another produces hypermotility of the intestinal tract, in particular the stomach. Such stimulation has yet another action, upon the blood vessels, which it dilates. Indeed some workers have discovered small delineated hyperaemic areas at the termination of small arterioles with submucous extravasation after stimulation of the vagal centres. (67)

(b) Chemical Control of Gastric Acidity.

A.C. Ivy with his numerous associates in Chicago is the great champion of the "Humoral Theory" of the control of gastric secretion and that such a mechanism exists he has proved beyond any reasonable doubt.

The crucial experiment was one in which a pouch was constructed from the stomach of a dog. All connections with the stomach, including extrinsic nerves, were cut except a vascular pedicle. The pouch was implanted subcutaneously so that secretion could be collected from it. After an adequate time had been allowed for a collateral circulation to have formed, the original vascular pedicle and with it any remaining extrinsic (sympathetic) nerves were cut. The pouch was therefore totally devoid of any extrinsic nerves and its original blood supply.

Such a pouch was found to secrete a juice containing/



containing acid after a meal, and after histamine and gastrin administered subcutaneously. It does not show any appreciable fluctuations in the continuous secretion apart from the stimulation of eating. This "resting secretion" never contained free acid and only a very small amount of total acid.

Mechanical distension with a balloon produces a secretion of mild digestive potency. (68)

Mechanical or chemical irritation of the mucosa of the stomach or of a transplanted stomach pouch also produces a secretion, but it is of low acid and enzyme value and contains much mucus. (41) (12) (69)

The only conceivable way in which a completely transplanted and denervated pouch such as Ivy used can receive stimulation from a meal taken per vias naturales is through its blood supply.

The interaction of food in the stomach and/or duodenum with the secretion there present produces a substance "gastrin" which is of an histamine-like nature (or is even histamine itself). This gastrin is absorbed into the blood stream and eventually reaches the intrinsic secretory mechanism of the stomach or pouch. The actual flow of secretion is probably caused by stimulation of the ganglia of the parasympathetic system. (See Page 21). These ganglia are in the stomach wall and in the intact stomach, vagal fibres arborize round them. Section of/

of the extrinsic nerves however, although removing any outside nervous stimulation would not cause degeneration of the ganglia themselves, which are different neurones. (70)

It must now be seen that Nervous and Humoral Mechanisms for the control of gastric secretion are both operative and must be regarded as complementary to each other and not considered as contradictory alternatives as has been done by so many workers in the past.

(2) ACUTE ULCERS CAUSED BY
NERVE INFLUENCES.

In the last few pages we have seen that experimentally many of the concomitants of chronic ulceration of stomach or duodenum in man can be reproduced in cats and dogs by overaction of the vagus - Hypersecretion, Hyperacidity, Hypermotility, Pylorospasm. It only remains now to add that actual ulceration of stomach and duodenum may also be produced by interference with the autonomic nerve supply. At first sight it would seem then that the problem of ulceration was more or less solved. But it is not so; for although acute ulceration may be produced by very numerous means, 50 according to Pulvertaft, (71) neurogenic and otherwise, no consistent method of producing chronic ulceration in experimental animals physiologically resembling men, short of extensive operative interference with the normal continuity of the alimentary tract has yet been discovered.

Ulcers closely resembling chronic "peptic" ulcer in man have been produced by the operation of Internal Duodenal Drainage (57), but in this manoeuvre gross mutilation of the normal anatomical and physiological relations takes place, and this reduces considerably its aetiological significance. Gastric ulcers with a degree of chronicity have been produced in the rabbit/

rabbit by section of various autonomic nerves and also by electrical stimulation of the vagus, immediately below the diaphragm, through an insulated electrode led out on to the animal's back, with a weak faradic current for 10 minutes daily for 10 to 26 days.

The rabbit however, is an animal very prone to develop erosions in its upper alimentary tract; and its so-called stomach is really a paunch and not in any wise comparable to the human stomach. (72)

Up to date, an acceptable and satisfying explanation of chronic ulceration has not been attained and the subject still remains a highly controversial one. If one could reproduce chronic ulceration in stomach or duodenum of dogs, cats or monkeys by a standard method not interfering with the health or general continuity of the gastro-intestinal tract a great advance would undoubtedly be made, and it is this problem which still flaunts itself before the eyes of the experimental surgeon. The Neurogenic Theory certainly explains away more of the facts relating to chronic ulcerative disease than any of the popular but ephemeral local theories. Our recent advances in knowledge of the Autonomic Nervous System is rapidly adding substantiation to the once highly speculative theory, and it is along nervous lines that the final explanation must be sought which will unify the present distressing controversies and variations in both surgical and medical treatment.

Acute/

Acute erosions of stomach and duodenum in both man and animals are very common, but these heal rapidly and often produce no symptoms. (12) As chronic ulcer no doubt follows the non-healing of one of these it would be profitable to enquire into a common causative factor of the production of both acute ulcers and the known concomitants of chronic ulcer—as already enumerated, (Page 30). Rokitansky as long ago as 1841 hit upon this factor. (2) He described with great clarity, acute perforating ulcers, haemorrhagic erosions and simple chronic ulcer. He also described two forms of acute softening which he sharply distinguished from post-mortem, or self digestion, of the stomach. The first, a gelatinous softening, occurs in the new-born and is frequently associated with a demonstrable intracranial lesion (often a tentorial tear), so, "the proximate cause may be looked for in diseased innervation of the stomach, owing to a morbid condition of the vagus, and to extreme acidification of the gastric juice." The second form of softening, he distinguishes two types: one of them "occurs, both in children and adults, as the sequel of acute affections of the brain or its membranes, and is probably brought about by a reflex action of the oesophageal and gastric branches of the vagus"; in the other type associated with cachectic states the stomach contains large amounts of "coffee-ground" fluid/

fluid which is often vomited during life.

It is a pity that Rokitsansky was so quickly followed by Virchow whose fame caused many of the latter's theories to have an uncritical acceptance for many years after his death. Thus his theory of thrombosis in the vessels of the gastric wall as the cause of ulcer, started off the exclusively local, and also very restricted and unprofitable search for the primary cause in the stomach wall itself which has delayed so long, wider progress.

Cases have been published from time to time during the last century in which the association of gastro-duodenal ulceration and haemorrhage with disease of the nervous system, mainly the brain, had been noted. (see Page 6). (73) (74) (75)

In 1910 it was suggested that gastric and duodenal ulcer was a secondary disease, the primary disease being situated at some distance away from the stomach not in the direct course of the gastric nerves, and bringing about ulceration by reflex and not direct irritation of the vagi. (See Page 6) (8) (10) With this idea in mind it was reported from Berlin that of all the ulcers seen post-mortem for 4 years 17% were associated with affections of the brain; a greater percentage than that in which cardiovascular disease, tuberculosis or cholelithiasis was considered/

considered to form the "primary" disease. (76)

And so on one could go quoting cases in which the association of gastric erosions and haemorrhage or even chronic ulcer with lesions of the brain affecting medulla or hypothalamus is much too frequent to be a fortuitous occurrence. After reading the excellent article by Harvey Cushing on certain of his own intracranial cases associated with gastric erosions and his summary and discussion of the experiences of others, there can be no doubt acute ulcer is caused by irritation of the parasympathetic system anywhere in its course from the hypothalamus to its vagal terminals. (15)

(3) OTHER THEORIES OF THE AETIOLOGY OF
"PEPTIC" ULCER.

(a) INFECTION.

It has been stated that organisms from a distant focus may settle in the gastric mucosa and produce ulceration. Indeed the same type of organism (a streptococcus) has been implanted in the teeth and subsequently found in a duodenal ulcer. Also organisms of the same type have been isolated from appendix, gall bladder and gastric ulcer in the same case. (77) (78) It is certainly likely that the streptococcus is a secondary infector considering its frequent presence in the alimentary tract, but that it is the original cause or even one of the original factors is still very debateable and many people believe that there is no satisfactory evidence at all for the assumption that infection is a primary cause. (79)

(b) PECULIARITY OF BLOOD SUPPLY.

It has been shown that the blood supply to the duodenum is rather precarious and in fact the anterior wall of its first part appears to be supplied by what is virtually an end artery. (80) It can easily be seen then that embolism, thrombosis or spasm affecting this region could well leave an ischaemic, devitalised part of duodenal wall to fall a prey to the digestive acidity of the gastric juice.

(c) DEFICIENCY IN CERTAIN CHEMICAL SUBSTANCES.

In 1935 and 1936 the medical world was filled with a great hope that the ideal treatment of "peptic" ulcer had been discovered after the publication of Aron and Weiss' article on the Histidine Injection Treatment. (81) But that hope was not justified as shown by subsequent series of cases.

I had the opportunity of personally carrying out the treatment in 15 cases of ulcer. In 14, even after one, two or three injections of Histidine (La Roche) symptomatic relief was very great, and by the end of a 3 week course, the whole 14 were symptomatically cured. One case, a chronic alcoholic, was refractory and admitted only slight relief in his symptoms. In two cases only were there definite radiological signs of healing. Six cases relapsed within 3 months.

Those observations, that in many cases early relief from symptoms is striking but that permanent cure is rare, have been noted by many observers. (82)
(83)

From these results in man and from the original experiments in the prevention of ulceration in Mann-Williamson dogs (57) it appears that histidine has some anti-ulcerative power but the evidence that a deficiency of the substance is the cause of peptic ulceration/

ulceration is highly circumstantial.

Nevertheless it forms a useful adjuvant in the treatment of cases where pain is a prominent feature particularly where combined with strict dietetic measures.

(d) HYPERSENSITIVITY.

It has been suggested by some authors that a patient may become sensitized to certain foods or animal emanations and ulceration of the stomach be caused much in the same way as bronchial asthma and certain types of dermatitis.

Some experimental evidence for such a possibility does exist. By injecting some gastric cells of a guinea pig into a rabbit, the rabbit's serum eventually contains a guinea pig gastro-toxic factor so that if the rabbit's serum is injected into a guinea pig, ulcers of the stomach develop which bear some similarity to the subacute variety in man, but do not exhibit the cellular infiltration which is so characteristic. Similarly gastro-toxic serum for the cat may be prepared by passing cat stomach cells through a goat. This principle has been fully worked out by many serologists but it is not now believed that it can be operative except in a very few cases at the most. (84) (85)

(e) VITAMIN DEFICIENCY.

The deficiency in vitamins is one of the most recent suggestions as to the cause of chronic ulceration. That it may be one of the factors in the continued non-healing of ulcers under the usual dietetic treatment is certainly likely because the average ulcer diet is very poor in Vitamin C, the deficiency of which gives a sub-scorbutic tendency and may be responsible for continued melaena under medical treatment, or to haemorrhage from the suture line of an anastomosis in patients who have had prolonged medical treatment pre-operatively.

Lack of appetite or deficiency of absorption from disorders of the alimentary tract apart from ulceration may be considered an initiating factor in some cases, while in others, primary dietetic deficiency is suggested. (86)

Small degrees of Subvitaminosis B and C are estimated to be relatively common, in Britain at least, and this may easily lead to gastro-intestinal disorders, loss of appetite, indigestion and constipation (87) and may therefore be a factor in tipping the balance of health over in the wrong direction as it were, or allowing an acute ulcer of the stomach or duodenum which is a common accompaniment of various disorders (12) to become a chronic ulcer.

VIII. AUTONOMIC IMBALANCE.

(1) EXPERIMENTAL.

In the preceding pages I have presented many facts and made several deductions in relation to the problem of chronic Gastric Ulcer and Duodenal Ulcer which are very suggestive and support the Neurogenic Theory. However, rather than take refuge in mere deduction, is there not some further experiments or observation that can be made which would bring us nearer to writing quod est demonstrandum to the Neurogenic Theorem?

Three lines I think may be followed up with advantage:

- (a) The method of animal experiment has been tried on many occasions and although much that is useful has been learned, the problem of creating a chronic gastric or duodenal ulcer in cats and dogs (animals which resemble man closely in their autonomic distribution and gastric physiology) is still unsolved. Descriptions of my own experiments directed towards this end will follow - experiments be it said still unsuccessful in their ultimate goal, but still, incomplete - and still hopeful.

(b)/

- (b) The method of Biological Proof may be essayed.

Section of the nerves of the stomach in man has been done on numerous occasions, mainly by continental surgeons, for one reason or another, and examination of the pre- and post- operative findings in these cases should add something to our knowledge both of aetiology and possible improvement in the routine treatment of certain types of gastro-duodenal disorder.

- (c) Some information also may be gained from observation on medical cases in which drugs known to mimic the action of parasympathetic or sympathetic stimulation (e.g. pilocarpine or atropine) have been used.
-

(a) Animal Experiments.

It will be realised that to arrange for continuous stimulation of a nerve, or indeed frequent stimulation of a nerve throughout a period of weeks is a very difficult matter indeed, and the experiments described along this line are very few, the number of entirely successful experiments being exactly nil. To produce paralysis of a nerve is on the other hand, very easy, and consequently it may be truly said of experimenters exploring the physiology of the autonomic system in this manner, their name is legion.

And it is true to a great extent that withdrawal of sympathetic stimuli from a certain region of the body by means of sympathetic nerve section produces a relative overaction of the other part of the autonomic supply, to wit, a localised vagotonia. In like manner sympathicotonia may be produced. Results of a few of the main workers in this field whose results would appear to be of value in our enlightenment will therefore be considered.

In 1906 Cannon using cats, and cutting the vagi in the neck below the origin of the laryngeal nerves and using X-rays to assess the effect on the stomach noted that little change was observed except a delay in emptying time at the end of a month. Transperitoneal/

Transperitoneal section of the splanchnic nerves appeared to produce no change, and a combination of both methods resulted in slight delay of emptying. (88)

Carlson published his experiments on 12 dogs. The vagi were cut in the thorax and contraction of the stomach studied by means of balloons residing in its lumen, passed either by the oesophagus or through a gastric fistula. The animals were studied up to 3 months and hypotonus noticed. Transperitoneal splanchnic section produced increased tonus with more frequent contractions. Combined vagotomy and splanchnotomy also gave hypotonus with increase in both rate and force of the contractions of the stomach. (89)

Litthauer using 22 dogs reported dilatation of the stomach in 9 out of the 22, atony in a like number, diminished motility in all, with delay in final emptying time. The vagal section was done either in the neck, thorax or subdiaphragmatically. Splanchnic section in the thorax decreased the emptying time. These were assessed by the amount of bowel content recovered from duodenal fistulae. (90)

Stierlin performing subdiaphragmatic vagal section and/or extirpation of the coeliac plexus in dogs, confirmed closely the results of the last worker, by X-ray examination. (91)

Nieden found a slight hypotonus on vagotomy and possibly a slight delay in emptying. Similar results were obtained in section of both vagal and sympathetic fibres whereas no effect seemed to be produced by splanchnic section alone. (92)

And so the results accumulate through the work of K  nnecke, Latarjet, Watanabe, McCrea and Hughson who all report results along the same lines but always with some little point of difference that does not seem quite to fit in. (93) (11) (94) (13) (95)

However, if one remembers how easy it is to get irritation at the cut end of a nerve, and how simple to miss a small splanchnic root which is then caught up in fibrous tissue with irritative results, a very probable explanation is offered for the variation in results without having to invoke the possibility of personal error in observation.

Nevertheless in spite of some differences the great majority of experiments show that for several months at any rate, vagal section diminishes tone, increases the initial emptying time due to the semi-patulous condition of the pylorus, but ultimate delay owing to diminished stomach contractions and less vis a tergo to the gastric contents.

Section of both vagi and splanchnics produce results/

results similar but less intense than above, whereas splanchnic section gives the exactly opposite effects. The inosculation of the right and left vagi is so profuse that one nerve is quite capable of carrying all necessary stimuli to the whole stomach and so it is an observation common to all workers that section of only one vagus nerve, unless possibly made at the extreme peripheral reach of its course, is without observable result. Splanchnic section is followed occasionally by small erosions in stomach or duodenum in the cat or dog, but vagotomy seldom if ever produces such a result except in the few days immediately following operation when the result is then clearly due to the shock or irritation of the cut nerve before peripheral degeneration.

By simple deduction it will therefore be seen at once that the action of the vagus is to keep up the tonus of the stomach, delay the immediate overflow of gastric contents into the duodenum, presumably to allow of digestion proceeding to a certain degree before the food reaches the intestine, but to assure the ultimate complete emptying of the stomach in a reasonable time after a meal, by keeping up good peristaltic waves.

That those effects are not entirely permanent also shows the presence of a good compensatory mechanism, residing within the stomach wall itself since the/

the organ ultimately works well after all extrinsic nerves have been severed. (The enteric plexuses of Meissner and Auerbach).

In rabbits however the position is quite different; but so is the anatomy and physiology, and thus little comparison can justifiably be made with results in man or animals of similar gastric physiology such as the cat and dog.

Mucosal haemorrhages and in some instances actual erosion were produced by vagal section - Lorenzi. (96)

Chronic ulcers in the pyloric region in 10 out of 20 rabbits have been produced by bilateral vagal section - Yzeran. (97)

Resection of both vagi subdiaphragmatically produced gastric ulceration in 6 of 18 rabbits in 24 days - Ophuls. (98) (99)

Greggio also by section of the vagi induced gastric ulcer in a few instances in rabbits which had some characteristics of chronicity. (100) (102)

Vedova and Durante (101) produced so-called chronic and acute ulcers in the stomach by resection of the splanchnic nerves.

In fact even opening the abdomen and shutting it up again would appear to produce an ulcer in some of these animals.

Although the literature on the motility of the stomach is so great, that on secretion in relation to the autonomic nerve supply was very scanty till a few years ago.

In 1927 de Vecchi states that in operations on dogs done by Foa, resection of the sympathetic nerves at the pylorus produces considerable heightening of the acid level of the gastric juice above the previously ascertained normal for the particular animal. In other dogs section of the vagi lowered the acid level greatly and a combination of both methods produced a slight diminution of Hydrochloric acid. (103)

In 1929 Hartzell published some very long and painstaking experiments. He trained dogs in the art of swallowing a stomach tube and discovered that at the end of 6 weeks they could do it very well, in fact rather liked it. The dogs were given meat test meals and specimens of gastric content withdrawn at frequent intervals through the swallowed tube. The acid curves thus obtained became very constant for each individual dog at the end of 6 weeks whereas during the first few weeks the animals had not become accustomed to the procedure, were somewhat upset, and this gave a lowering of the acid and an increase in the mucous content.

The/

The trained and standardised dogs were then subjected to a bilateral transthoracic vagal section. Every dog showed great decrease in both free and total acid curves obtained, for many weeks after the operation. In fact the highest post-operative fractional test meal curve was lower than the lowest pre-operative curve. There was only one exception, a dog in which the pre- and post-operative curves were much about the same. When this dog came to post-mortem, it was found that the posterior vagal trunk was still intact, thus explaining the apparent anomaly. (104)

The splanchnic nerves are probably both secretory and inhibitory. Thus electrical stimulation of the splanchnics or of their centres even as far back as the posterior hypothalamus produces a secretion of mucus by the stomach and at the same time a considerable diminution of acidity, more than can be accounted for by the combination of acid with the mucus.

Bilateral division of the splanchnics or ablation of the coeliac plexus causes a very watery gastric juice of high acidity to be secreted as has been shown by Moll and Flint amongst others. Collateral evidence that the sympathetic system is responsible for lowered acid secretion is given by the fact that sufferers from hyperthyroidism usually have hypo- or even achlorhydria. Also thyroid feeding experimentally lowers gastric acidity in dogs. (105) (16)

Little or no difference follows section of the vagus in dogs according to Friedenwald and Feldman.(99) They base their conclusions on the results obtained after operating on dogs and assessing the gastric secretion by the use of a 7% alcohol test meal plus the subcutaneous injection of $1\frac{1}{2}$ mgm. of histamine. And the result is natural enough considering that alcohol has a direct action on the mucosa itself while histamine stimulates the peripheral ganglia in the stomach wall and is known to produce secretion entirely independently of extrinsic nerves which also act on these ganglia!

It is also reported by Madelaine Brown (106) that removal of the sympathetic chains and coeliac ganglia in cats has no effect on the secretion of Hydrochloric acid by the stomach. And no wonder, for here again the criterion of secretion used was the histamine test meal.

The two last reports indicate well the pit-falls that await the investigators of this most complicated problem.

From animal experiments, the results of which appear at first sight so chaotic, it emerges quite clearly, if the results of those workers using faulty technique be excluded, that the vagus nerves are responsible for increased motility and increased acid secretion/

secretion of the stomach and bilateral section of these nerves produces relaxation of the pylorus, with hastened initial emptying time, delayed final emptying time, diminished peristalsis, a degree of atony and lowered secretion of juice, and lowered acid.

There is also evidence to show that these changes pass off to a great extent at the end of a few months and the previous "normal" state is approached. (107)

Results in these animals have been used to forecast the result of neurectomy operations in man and it has too frequently been stated that although some improvement may result from vagal section for a few months the late results will show little improvement.

But these conclusions are erroneous for in animals the sympathetic / parasympathetic balance is stable, nor do the experimental animals used suffer from vagotonia nor hyperchlorhydria nor "peptic" ulcer.

In man however, it is a previously pathological system, the effects of which a vagal neurectomy would cut out, that is being attacked and even should the initial results of vagal section pass off - as they will - a return will be made not to the previous pathological state but to the automatic normal of the stomach itself isolated from upsetting influences.

Hydrochloric acid will be secreted, but only in sufficient quantity to ensure the perfect digestion of the stimulating food, but totally unable to wreak evil work on the gastric mucosa.

(b) Neurectomy Operations in Man.

So convinced have British and American surgeons been in the past that the cause of "peptic" ulceration resided locally in the confines of the stomach itself that nerve section operations have rarely been done, and those that have been done were often based on erroneous anatomical and physiological principles or were otherwise unsuitable for the physical signs presented; and so operations from simple pyloroplasty to the severe mutilation of an extensive partial gastrectomy have held sway. Numerous continental surgeons however, have practised neurectomy operations, but unfortunately the value of their results from the experimental and aetiological aspect have not been great since manoeuvres such as gastro-enterostomy or partial gastrectomy have been done at the same time, making it thus impossible to assess from which part of the operation the good results came. However, a few simple neurectomy operations are reported in the literature.

In operating, attempt is made to do one of three things:-

- (a) To cut the main vagal supply to the stomach. The "left" vagus still retains its original "sinister" influence in the minds of some, and it was thought that/

that if the left nerve was cut the right did not matter much. But although what we now call the anterior gastric nerve (B.R. of B.N.A.) has larger branches to the stomach than its contralateral companion (O.T. right vagus), to consider the latter insignificant is surely quite erroneous.

(b) To cut the nerve supply to the pylorus.

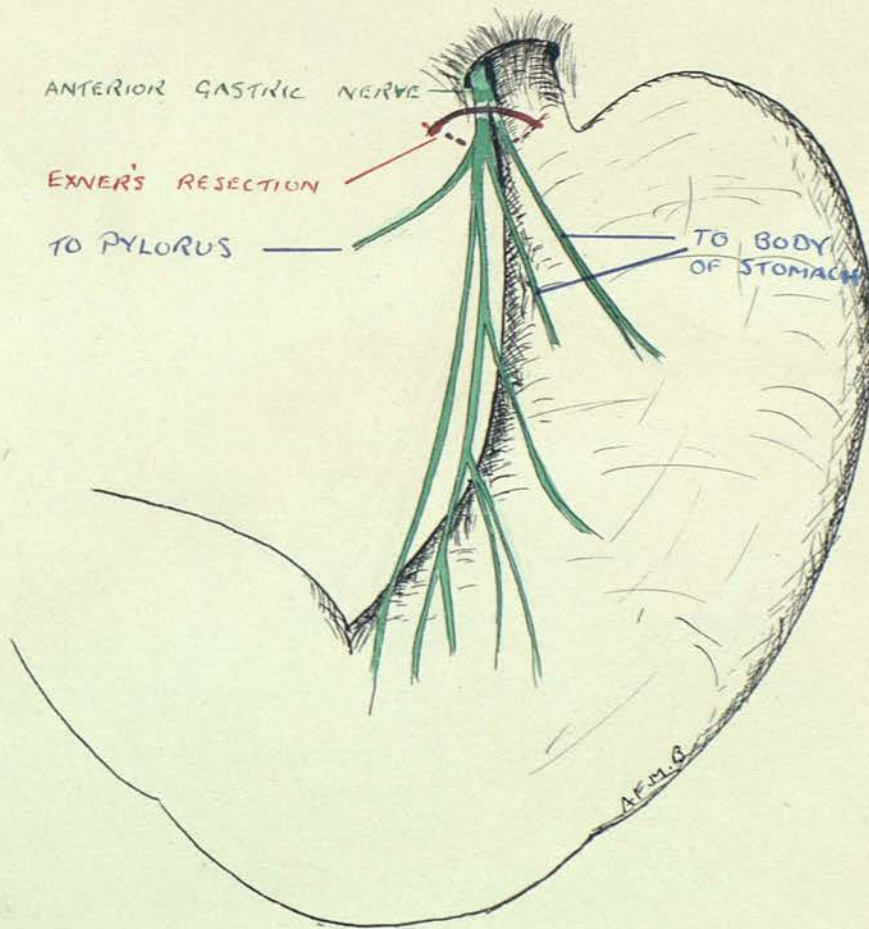
Resection of nerves on the lesser curvature has been suggested for this, but of course such an operation is quite wrong since the pylorus is supplied from above and no nerve runs along the lesser curvature to the pylorus.

(c) To denervate the stomach entirely, thus allowing it to fall back on its intrinsic automaticity and adapt itself to local conditions only, untroubled by higher control.

Subdiaphragmatic vagotomy had been done 14 times by Exner when he published his cases. (See Fig. 11) They were all tabetics with severe gastric crises. (These crises are due to irritation of the vagus either in its roots or nuclei and can be demonstrated pathologically. Severe spasm of the stomach can be seen radiologically).

7 were completely cured, 2 were greatly improved, in 2 the observation time only extended over a few/

FIGURE 11.



VAGAL NEURECTOMY AFTER EXNER

NERVES TO WHOLE OF FRONT OF BODY OF THE
STOMACH ARE DIVIDED. VAGAL PYLORIC BRANCHES
ARE ALSO DIVIDED AT THE SAME POINT

few months and was therefore not sufficient to say whether lasting cure had been attained. No apparent result followed in 2, while one case died before observations could be made. None were worse. (108)

Bircher (109) did an incomplete section of the vagi in 20 cases with clinical symptoms of gastric ulcer but which were mainly gastric neuroses with pylorospasm and secondary atony. All cases were stated to have given good results, and nausea, vomiting, pain & eructations disappeared. The hypersecretion and acidity were reduced and X-ray examination showed the stomach to be of normal tone.

Resection of the pyloro-duodenal nerves, and also other branches of the vagus and sympathetic by a submucous "circumcision" of the body of the stomach in the upper regions of the lesser curvature is done by Schiassi (110) who has formed a very favorable impression of suitable neurectomy procedures and reported many cures. An original report was of 2 cases treated as above whose cure was attained and the secretion of Hydrochloric acid was still notably diminished after a year and a half. (103)

In the post-war years, surgeons of the carnivorous or so-called radical order had their heyday and in America at least partial gastrectomy of formidable dimensions was considered the ideal treatment of nearly all gastric and duodenal ulcers. It was then considered/

considered that this operation produced anacidity or considerable hypochlorhydria and both cured the ulcer and prevented recurrence or complicating stomal (gastro-jejunal) ulceration. (111) (112)

But account had not been taken of the tremendous recuperative powers of the stomach which can apparently regenerate a very active acid secreting mechanism from quite a small piece of mucosa, (113) and more extensive follow-up of cases of partial gastrectomy showed disappointing recurrences and even gastro-jejunal ulcer.

If however one also does a section of the vagus nerves the results are much better and hypermotility and hyperacidity banished. (26) (114) (115) (116)

Latarjet of Lyons (11) reports 24 cases. His method of attack is a complete denervation, which is shortly as follows:- (See Figs. 12 & 13),

Through a high midline incision, the left lobe of the liver is retracted up and to the right with a broad flat retractor, the stomach is pulled downward, putting the lesser omentum on the stretch, and the anterior gastric nerve is defined at the upper part of the lesser curvature, where it can usually be seen easily if the anterior layer of the lesser omentum is carefully incised. A few centimetres of the nerve are resected, with or without ligating the left gastric artery.

The/

FIGURE 12.

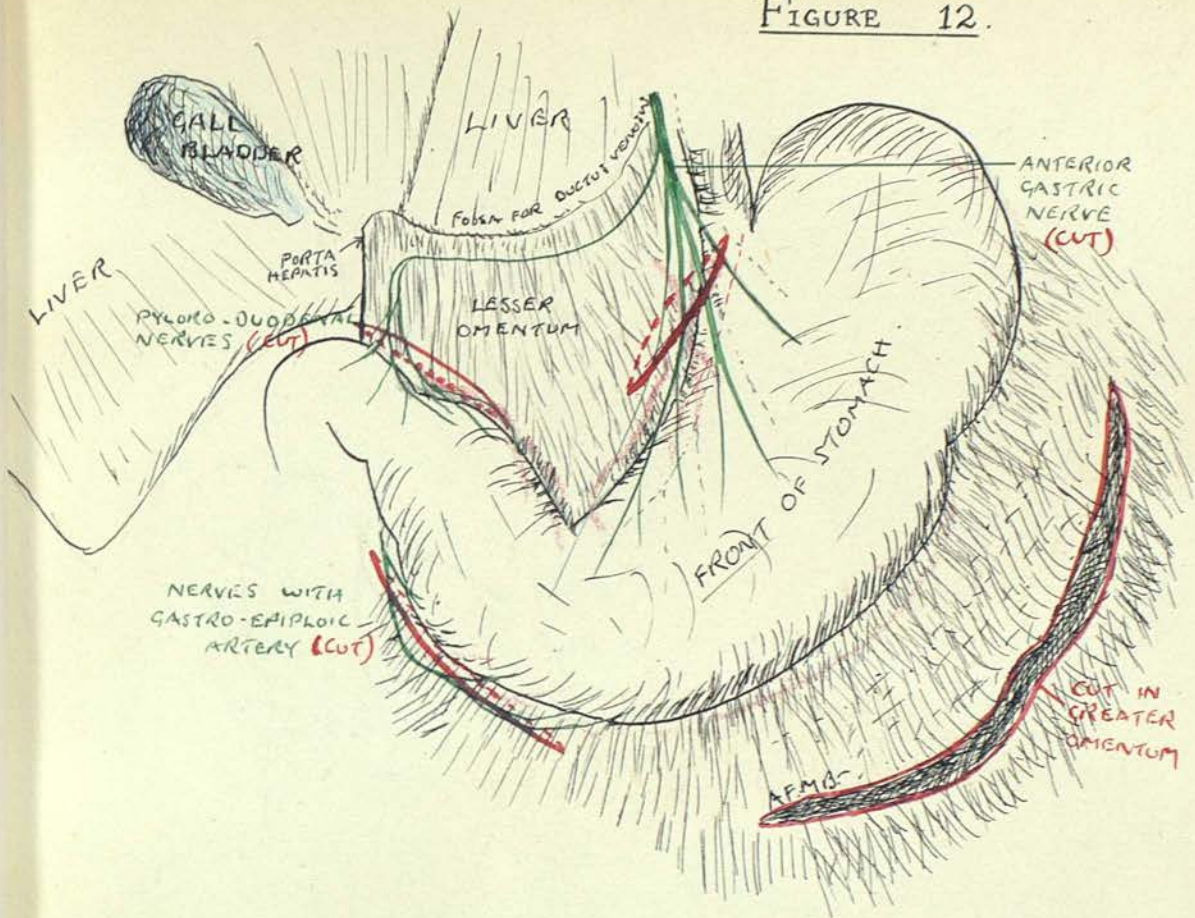
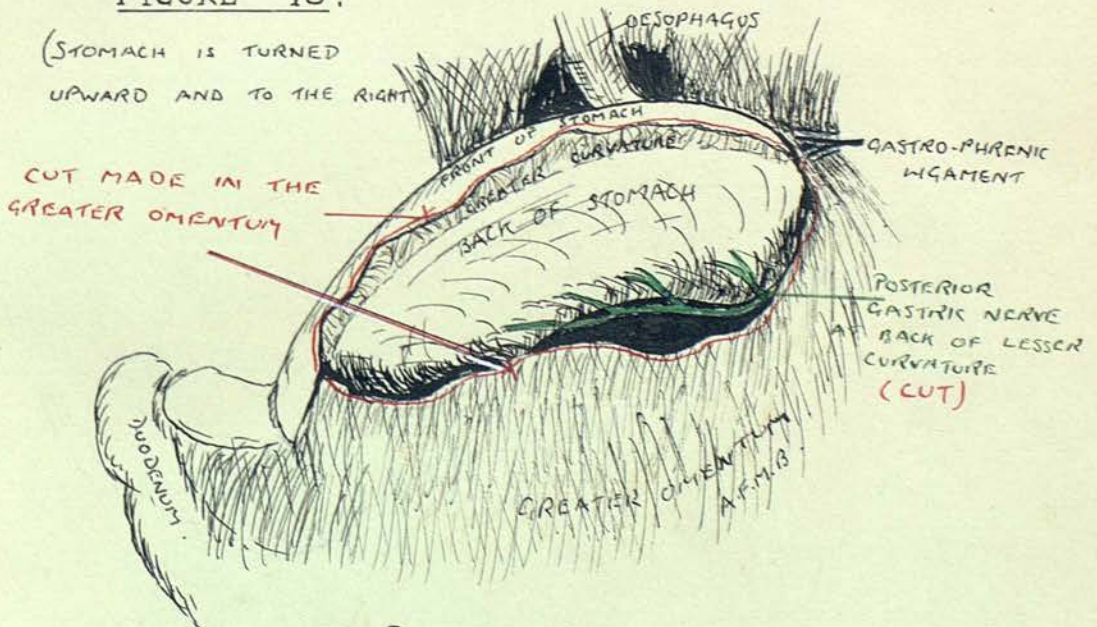


FIGURE 13.

(STOMACH IS TURNED
UPWARD AND TO THE RIGHT)



GASTRIC NEURECTOMY AFTER LATARJET.

NERVES CUT ARE MARKED IN RED.

RESULT IS AN ALMOST COMPLETE

DENERVATION OF THE STOMACH.

The anterior leaf of peritoneum just above the pylorus is incised and the nerve branches thus exposed immediately behind are cut as they enter the walls of proximal duodenum, pylorus and pyloric canal.

The anterior layer of the greater curvature is cut close along the wall of the pyloric antrum and a few nerve fibres accompanying the right gastro-epiploic artery are cut.

A considerable opening is made now in a relatively avascular part of the greater omentum and the whole stomach turned upwards, exposing its posterior surface through the aperture made. The highest accessible part of the back of the lesser curvature is reached and a portion of the posterior gastric nerve resected. The hole in the greater omentum is stitched up and the abdomen closed.

The operation is said to be quite a simple and quick proceeding in the majority of cases, but may have to be abandoned in cases, particularly of high gastric ulcer, with many adhesions or much infiltration and poor mobility.

Pain is severe for about 24 hours (presumably from irritation of the cut ends of the nerves) but is easily controlled by full doses of morphia. The stomach often shows considerable degrees of atony for a few days and may have to be washed out. (In some cases/

cases a gastroenterostomy was added because of this expected complication).

The operation was done for 3 types of case:-

Tabetic Crises.

Gastric Ulcer.

Gastric Neurosis (Gastropathies
he calls them.)

Gastroenterostomy was also done in most cases with the exclusion of the gastropathies.

At the end of six months all the cases appeared either completely rid or immeasurably alleviated of their stomach trouble. In particular, of the 18 cases which were subjected to denervation without other procedure, 14 were typed as "gastric neuroses" with disorders of motility and secretion and considerable symptomatic upset. 4 had tabetic crises. Of the neuroses, 13 seemed completely cured, and 1 had a slight recurrence of symptoms after 1 year. The tabetic cases all showed very great relief from both pain and vomiting. Observation was for periods of 6 months to 2 years and the results seem very creditable considering the rather neurotic type of patient these diseases occur in.

So much for the favorable or hopeful results of the few published neurectomy cases. It must be admitted that several (117) (91) (93) unfavorable reports/

reports have been made. If however the methods of operation are studied it will be seen that very frequently nerve section of any type has been looked on as a cure-all for all stomach disorders. In other cases vagal fibres have been cut when the condition was caused by sympathetic overaction and vice versa. Obviously results would be bad:if they had not been, the Neurogenic Theory could have been thrown on the scrap heap there and then.

(c) Related Phenomena: The Action of drugs.

It is now realised that autonomic action is carried out by means of chemical substances elaborated at the peripheral nerve endings - adrenaline in the case of the sympathetic and acetyl choline in that of the parasympathetic. Pilocarpine and physostigmine have choline-like actions which are not due to stimulation of the peripheral nerve mechanism but only to the prevention of the breaking down and destruction of the acetyl choline elaborated by parasympathetic nerves which is very quickly destroyed in the body.

It is also well known that some people are very sensitive to the action of pilocarpine and react violently even to small doses, and it is precisely the type of patient we have recognised as showing vagotonic tendencies that does react thus. The explanation is not far to seek: relatively larger amounts of acetyl choline are present in the body in consequence of the vagal overaction and when the normal breakdown of the substance is prevented by a small dose of pilocarpine a considerable excess of the acetyl choline^{is} available to act and so a violent parasympathetic action is produced.

Atropine/

Atropine is a sympatheticomimetic drug. Its action takes place very peripherally. It appears to paralyse the vagal terminals and antagonises the action of pilocarpine and physostigmine. It diminishes but does not completely abolish the action of histamine.

Nicotine is another drug that has been known for a long time to produce profound reactions similar to autonomic disturbance. Most people at one time or another have had an overdose of nicotine via a cigar or a pipe before a tolerance to the drug had been acquired, and they probably remember the most uncomfortable effects produced. At first the tingling feeling of warmth in the limbs, then the slight shivering and cold sweat that followed, the giddiness, the nausea, the excessive salivation shortly followed by vomiting.

All those symptoms are the same as is produced by stimulation of the parasympathetic system. Yet nicotine has been shown not actually to stimulate the parasympathetic but to paralyse the sympathetic, thus showing up the balance held between the two parts of the autonomic system. (118)

Further, to those with Gastric Ulcer or Duodenal Ulcer it is a well-known observation (though not always/

always freely admitted!) that smoking more than a very moderate amount immediately brings on an attack of epigastric discomfort if not heartburn, acid eructations or actual acid vomiting.

Experimentally, adrenalin is known to cause absolute relaxation and quiescence of the stomach, and according to most observers, considerable diminution of all secretion. (15)

Of a similar type to adrenaline only with a much more prolonged action is the drug Benzedrine. During the past year I have had the opportunity of observing its action in sea-sickness in persons of vagotonic tendencies and it is indeed remarkable how quickly the blood pressure and pulse rate rise to within normal limits, the greenish pallor disappears and nausea and vomiting are relieved and the whole abdominal turbulence settles. Further in two sufferers from chronic seasickness of my acquaintance, both showing some evidence of vagotonia, benzedrine, although taken in abject hopelessness and disbelief, proved a complete prophylactic even in a considerable seaway. (Reports of 100 cases of seasickness treated by Benzedrine have recently been published. (119)

Encouraged by this I administered the drug to 4 cases of duodenal ulcer in the Astley Ainslie Institution/

Institution that had failed to get relief even from the strictest of diets. In three cases symptomatic cure was obtained with lowering of gastric acidity in the fractional test meal and in the fourth, great amelioration of the symptoms.

In cases of irritable ulcer with spasm of the lesser curvature or pylorus, and high actively peristaltic stomach, benzedrine produces rapid and marked relief from that spasm as seen at screen examination during a barium meal. (120)

Thus another drug which appears to inhibit vagal action presumably by peripheral stimulation of sympathetic elements has been added to the armamentarium of the experimental pharmacologist.

Pituitrin is a curious drug in that its actions are different according as it is administered intraventricularly or by the more usual modes, subcutaneously, intramuscularly, etc. Intraventricular injection of even minute quantities produces profound vagal action with general sweating, prolonged vomiting and hyperactivity of the whole gastro-intestinal tract. This action is checked by atropine. It is interesting to remember that the hypothalamus is very close to the pituitary, indeed it is grouped round its stalk at the tuber cinereum. (15)

(2) SPONTANEOUS IMBALANCE OF THE AUTONOMIC
NERVOUS SYSTEM IN MAN.

It has been conveyed that organic disease in some part of the body intimately related with the vagus nerves or parasympathetic system was often strikingly associated with gastro-intestinal disorders, and it was this fact that intrigued the observers, such as Rokitansky and Rössle into speculating on the Neurogenic Theory.

However, if the theory postulated that disease of the stomach only followed organic disease of, or affecting by continuity of tissue, the parasympathetic nervous system it obviously failed to explain the cause of the majority of gastric and duodenal ulcers and the gastric neuroses. But we have known for several years now that the cranio-sacral "autonomic" nervous system of Langley and the thoraco-lumbar (sympathico-adrenal) system of Gaskell form one delicately balanced system, The Autonomic or Vegetative Nervous System. The actions of each part is either the direct opposite or in some cases the complement of the other. Moreover, the balance between the two is delicate and easily disturbed even in normal people, and furthermore a considerable proportion of all people have an inherent imbalance of the/

the system, usually the parasympathetic, but often the sympathetic factor, being more easily stimulated or continually overacting more than the other.

Thus as well as organic disease involving a part of the autonomic system we also have functional disorder, or to use the term applied to overaction of the parasympathetic system first introduced by Eppinger and Hess in their classical monograph on this subject - Vagotonia. All clinicians must have observed these functional types because it is with great frequency that patients show often many stigmata of the one or the other.

Now comes the crucial question, are these vagotonics liable to suffer from gastric disorders beyond the normal run of their fellows? And the answer is very clearly "Yes". Eppinger and Hess mention the fact that gastric disorder frequently is one of the complaints of their vagotonic patients but it was von Bergmann who first connected Vagotonia with organic disease of the stomach and set the seal of tenability on the Neurogenic Theory when he pointed out that even in the absence of pathologically demonstrable disease, in spasmodic "peptic" ulcer, there nearly always was present a functional disorder of the parasympathetic system, that patients with such an ulcer reacted to pilocarpine quite violently or/

or at least much more strongly than normal people and that continued use of atropine would create great symptomatic improvement. (10)

But before we go further, we must describe the Vagotonic Disposition (9) and in doing this the original description of Eppinger and Hess is so comprehensive and clear that it would be difficult to improve on in any but a few points.

"We have to do principally with youthful or middle aged individuals. Both men and women come to us complaining of some trivial symptom, stomach or intestinal trouble, fear of heart failure, or some "neurasthenic" trouble and are treated as ambulatory patients. The appearance of these people is that of "nervous invalids". Their actions are hasty and precipitous. The color of their faces is often very changeable, now flushed, now fading into paleness. A similar thing may happen when the patient is asked to undress. When they do this, blotchy areas of redness may appear on the trunk, and arms, which seems to be of considerable hardness. The hands of these patients are bluish-red, markedly cyanotic, getting pale when stroked with the finger, damp and cool. Of all these conditions the patient often makes mention. The palms have a thick skin, although the patient may not have been doing any hard work. These patients complain that they perspire/

perspire readily, and even over the entire body. In some there are places of predilection for the sweating which are quite characteristic (back, head, face, feet), and often during examination of this class of patients the sweat rolls from the axilla down the thorax.

Under the influence of anxiety or excitement, the face rapidly becomes moist, and drops of sweat appear on the forehead or nose after mild excitement. Sometimes one can recognise a vagotonic as he enters a room. Large, often beautiful eyes, which seem particularly large owing to the widening of the palpebral fissures, give the face the appearance that almost looks like that of Graves' disease. The eye glistens. Usually these people are undernourished, of inferior make up, who with their thick lips, plump nose and somewhat enlarged cervical lymph glands suggest that they may have had scrofula in childhood. Often the anamnesis justifies this impression. The skin of the back often shows fresh eruptions, often scars of an old acne, comedones, on the head, seborrhoea or scaliness is frequently found. The skin as a whole is moist and never presents the peeling conditions seen in old people, and in young people with severe diabetes."

The account then goes on to say how vagotonics are/

are often shortsighted, and can bring objects close to the eyes without blurring or double vision. Convergence is very strong and Moebius' sign never present. They swallow frequently while speaking and often have much saliva in their mouth. There is diminished sensitivity of the posterior pharyngeal wall (quite apart from any hysteric manifestation) but the tone of the rima glottidis is not diminished.

The respiration rate is variable, now sighing, now faint. Respiratory Arrhythmias are frequent, especially after a heavy meal. Sometimes they have a feeling of pressure in the chest and inability to breathe out. Great variation in the position of the diaphragm may be noted from day to day.

"Also, in the epigastrium and at the apex, a marked pulsation is noticeable, as is found when severe damage to the heart exists. The apex beat may be heaving and hard to depress, without there being any anatomical lesion of the heart. The heart sounds are clear, loud, often split and rapid, the pulmonary second sound much accentuated and sometimes also split. Percussion shows no abnormalities. Only when the pulmonary hepatic border is particularly high can one find a slight increase in the dulness to the right

The activity of the heart, as shown by its rate may vary greatly the patients will often/

often say that the rate of their heart increases, paroxysmally and that it is in these periods of relief from bradycardia that they feel better. At times, there is a feeling as if the heart would cease beating entirely, or that it is very irregular

Small and large pulsations follow one another, not always in rhythmic sequence, and very slight exertion as, for example, getting up or walking about, suffices to cause a sudden transition from bradycardia to tachycardia."

The vagotonic declares that large pieces of food stick at the back of the heart after swallowing. Soon after beginning a meal feelings of fullness and distension come over the patient though his appetite is not yet appeased. Sometimes the abdomen is seen to swell in the gastric region under the left costal margin. Relief is obtained by belching which is brought about by taking bicarbonate of soda. Others complain of acid retching which may even attain the severity of heartburn. The appetite is variable though generally very good. The activity of the bowels is sluggish, yet now and then there are unaccountable attacks of diarrhoea Stools are few in number and seldom bulky splashing in the region of the stomach directly after eating or after drinking a great deal of fluid is also very infrequent.

Vagotonics pass their water in small amounts and at frequent intervals. It is as a rule brightly coloured and may precipitate out a sedimentum lateritium in cold weather. Frequently an abundant nebula is found. Besides this the urine is rich in oxalic acids. It is sometimes excreted as a cloudy fluid due to an overabundance of phosphates, or, at least, precipitates the phosphates after excretion.

These urinary conditions are associated with urinary hyperacidity. This seems all the more probable since it is just where gastric hyperacidity is found that we run into these conditions. Usually there is found also an excess of carbonates in the urine and particularly after meals it may form on addition of acids. In many cases there is slight dysuria, the patient having to strain or to wait a few minutes before the urine can be voided. Other patients declare that the stream is broken. Dribbling after micturition has ceased is often admitted after questioning.....

The vagotonic is often sexually very excitable. Erections of the penis are frequent though of short duration. Premature ejaculations often occur. Others complain of frequent pollutions. Certain nervous stigmata are almost always present. The tendon reflexes are increased. Sometimes Chvostek's sign may be/

be obtained. The cremasteric, abdominal and muscle reflexes are active. Tremor of eyelids and tongue, as well as of the extended fingers is almost never absent. Dermatographism is usually marked."

The description is ended with the statement that bradycardia after pressure on the eyes, or stimulation of the nasal mucous membrane by ammonia, tobacco smoke, etc., often occurs; the tone of the sphincter ani is increased; the blood may show an eosinophilia; Vagotonia may be a family stigma and cases have been found in some of which the cranial, in others the sacral parts of the autonomic system, or even smaller divisions of these parts themselves show the most marked signs of irritation.

The above is the picture of vagotonia developed to its fullest extent, but there are all grades and the slight or medium types are quite common. Indeed one only needs to think on the various patients one has treated for gastric disorder (other than simple gastritis) to remember that a very considerable proportion of them showed numerous signs of vagotonia.

Several times now a series of fractional test meals has been done on apparently normal healthy people with no sign nor symptom of gastric disorder. It is a unanimous finding that although the majority show a gastric acidity curve and volume of juice which/

which falls between two lines, the bounds of which may be considered as the limit of normality, there is a definite percentage whose gastric acidity is constantly above or below that normal.

Thus in 100 students who had never suffered from any gastric disorder 80% fell within two comparatively narrow limits. The usual gruel fractional test meal was employed and specimens withdrawn at quarter hour intervals for $2\frac{1}{2}$ hours by indwelling Rehfuess tube. The maximum readings obtained were:-

Fasting: 22 cc. decinormal Hydrochloric acid per 100 cc. of gastric contents and during the meal, in the $1\frac{1}{2}$ hour specimen 45 ccs. $\frac{N}{10}$ Hydrochloric acid per 100 cc.

The minimum result was 0 cc. Hydrochloric acid in the fasting juice and 12 cc. decinormal Hydrochloric acid per 100 cc. gastric content in the $1\frac{1}{4}$ hour specimen.

(See Fig. 14.)

Of the remaining 20% approximately half had readings above the arbitrary normal and half below. Of the half below 3% showed total achlorhydria. (121)

(Figs. 15, 16, 17.)

The advantage of taking a group of people whose average age is low (between 20 and 30) is that diseases to which there may be an inborn predisposition (gastric and/

GASTRO-INTESTINAL ANALYSIS.

Name of Patient

Ward

Bed

I. FRACTIONAL TEST-MEAL. Date.

Fasting Juice.

Volume.

Cells.

Fasting $\frac{1}{4}$ $\frac{1}{2}$ $\frac{3}{4}$ 1hr. $1\frac{1}{4}$ $1\frac{1}{2}$ $1\frac{3}{4}$ 2hr. $2\frac{1}{4}$ $2\frac{1}{2}$ $2\frac{3}{4}$ 3hr.

Mucus

Bile

Blood

Starch

100 (-364)

90 (-327)

80 (-292)

70 (-255)

60 (-219)

50 (-182)

40 (-146)

30 (-109)

20 (-073)

10 (-036)

 $\frac{N}{10}$ NaOH (%HCL) $\frac{N}{10}$ HCL.NORMAL HUMAN
LIMITS FOR
FREE HCL.

The shaded area represents the limits for free HCL. in 80% of normal people, and average rate of emptying (2-2½ hours).

RED HORIZONTAL SHADING represents free HCL, WITHIN NORMAL LIMITS.

— represents total acidity.

HIGHEST "NORMAL"
FREE HCL.
4.5cc $\frac{N}{10}$ HCL approx
per 100cc GASTRIC
CONTENT.

One Hour Fraction.

Free HCL.

Active HCL.

Total Chloride.

Summary.

NORMAL LIMITS OF FREE HYDROCHLORIC ACID (HUMAN)

(AFTER BENNETT AND RYLE)

2. FÆCES.

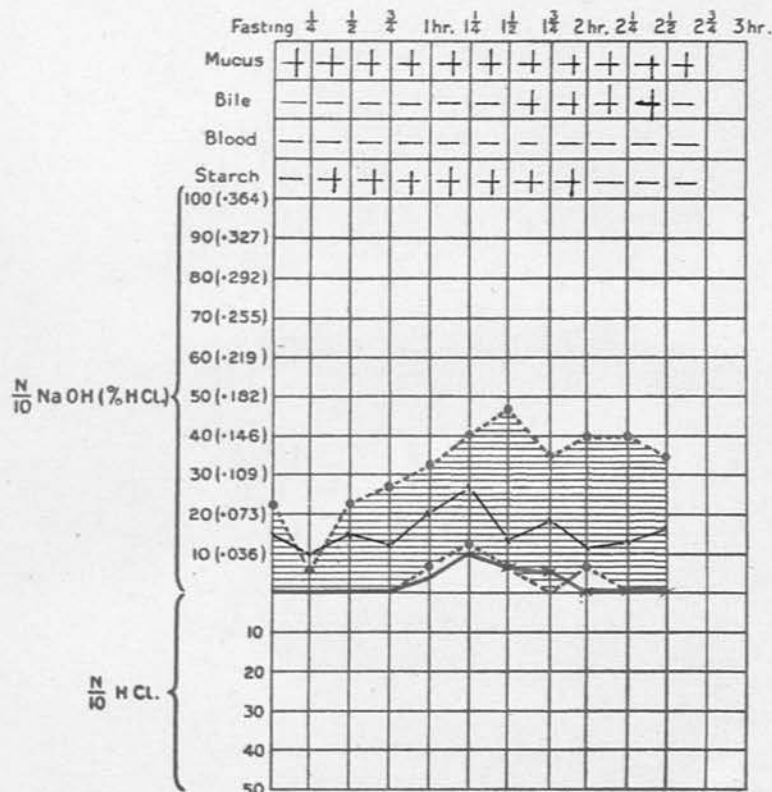
GASTRO-INTESTINAL ANALYSIS.

Name of Patient MRS. MARY W — Ward 25.

Bed

I. FRACTIONAL TEST-MEAL. Date.Fasting Juice.Volume. 8 cc.

Cells.

One Hour Fraction.

Free HCl.

Active HCl.

Total Chloride.

The shaded area represents the limits for free HCl. in 80% of normal people, and average rate of emptying (2-2½ hours).

RED represents free HCl.

BLACK represents total acidity.

Summary.HYPOCHLORHYDRIA.2. FÆCES.

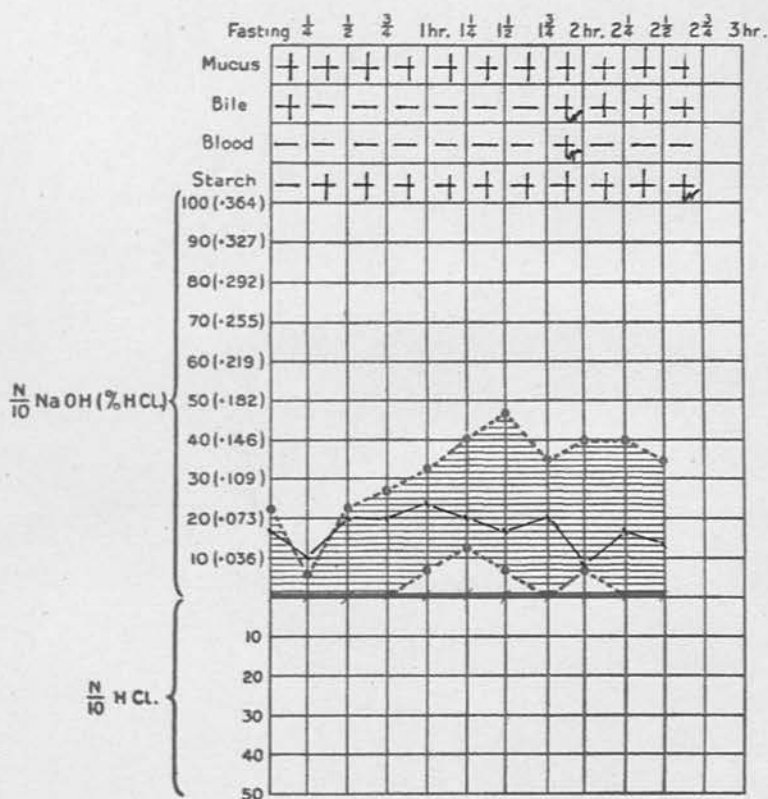
GASTRO-INTESTINAL ANALYSIS.

Name of Patient MRS. MARY D Ward 25

Bed

I. FRACTIONAL TEST-MEAL. Date.Fasting Juice.Volume. 5 cc.

Cells.

One Hour Fraction.

Free HCl.

Active HCl.

Total Chloride.

The shaded area represents the limits for free HCl. in 80% of normal people, and average rate of emptying (2-2½ hours).

RED represents free HCl.

BLACK represents total acidity.

Summary.ACHLORHYDRIA.2. FÆCES.

and duodenal ulcer I am convinced fall into this category) have for the most part not yet developed, as they will do later, due in part to the stress and strain of modern life. The alternative of taking a series of healthy people of all ages therefore would not give such an accurate index of the proportion of those with inborn abnormal tendencies because many would already have developed the disease to which they were predisposed and therefore would be excluded among a group "healthy people". (122)

Thus in Vanzart's series it is stated that "there was a steady increase in the incidence of achlorhydria from youth to old age. At the age of 60 years 28 women in 100 failed to show free acid and similarly 23 men in 100 were achlorhydric....."

How do we account for the decrease in the percentage of people with "silent" hyperchlorhydria and the increase of those with achlorhydria? Is it not that many have already developed symptomatic gastric ulcers or duodenal ulcers or have had their acid lowered by gastritis which the gastroscope has shown to be a fairly common symptomless disease in middle and late life, and are therefore not included in Vanzart's series but are in Ryle's?

Moreover those people with hyperchlorhydria show, in a far greater proportion of cases than those with normal acid, other signs of the vagotonic disposition as/

as already indicated. Many too have a high actively contracting "steerhorn" stomach.

In fact some writers have gone as far as to say that the vagotonic disposition or "Hypersthenic Diathesis" is accompanied not only by functional disturbances but is characterised by actual physical conformation. Thus Hurst describes his hypersthenic diathesis as being accompanied by shortness of stature and a wide costal angle while the opposite type, the hyposthenic diathesis is long and thin with narrow costal angle and a tendency to visceroptosis.

Others have even gone further and "diagnosed" gastric and duodenal ulcer from obscure anthropometrical data such as dental spacing, mental and mandibular angles. (123) But these conclusions are perhaps a little far-fetched or at least too advanced for present methods of clinical proof to cope with!

Another series of Test Meals done on 100 normal students supplies some interesting data.

Eight students who in subsequent careful questioning admitted occasional attacks of slight dyspepsia showed an increase both in the volume of gastric juice and the amount of free acid.

Twenty students of the hundred who had had no gastric disorder whatsoever had increased gastric secretion/

secretion and increased amount of acid from the arbitrary normal. In each case it emerged that one or both parents or near relations (aunts or uncles) had long dyspeptic histories often with actual Gastric Ulcer or Duodenal Ulcer. It was quite the exception to find this in the history of the students with a normal acid curve. This seems an indication that hyperchlorhydria and "peptic" ulcer is a hereditary disease or at least a hereditary constitutional tendency exists. There is one possible fallacy in the implication, however; both parents and son may only be suffering from the culinary indiscretions of family cook! (124)

(3) ACQUIRED IMBALANCE OF THE
AUTONOMIC SYSTEM IN MAN.

(a) Organic Disease.

The disturbance of autonomic balance may be acquired throughout life. The most likely people to fall victims to this derangement are of course those with constitutional lability of the autonomic system to which further imbalance is added, but even strictly normal people may possibly be affected.

One of the most frequent methods of acquisition is by reflex irritation of the vagus by disease in a part of the alimentary tract distant from the stomach. The appendix is a very favorite site. The following is an illustration of such a case at the Victoria Hospital, Burnley:-

M - H - . Female. Age 28 yrs. A mill-worker, appeared at an out-patient clinic complaining of epigastric pain coming on about $1\frac{1}{2}$ to 2 hours after food. The appetite was quite good but very little food appeared to satisfy the patient and the pain was relieved greatly if not entirely. Not long after a meal the patient would become hungry again, and if not relieved the hunger would gradually get worse until definite epigastric pain developed. The attacks would last days or weeks and then disappear perhaps for/

for a month or two. The first attack was about 18 months ago.

On examination:- there was slight general epigastric tenderness. There was definite tenderness localised over McBurney's point. Pressure in the left iliac fossa caused discomfort in the epigastrium. Vaginal examination was negative.

Test Meal result ^{similar to} (Fig. 15) showed hyperchlorhydria with rapid emptying of food as shown by starch test.

X-ray Barium Meal: showed a high, active, rapidly emptying stomach. No organic lesion could be detected. Appendix was not visualised.

The patient was admitted to hospital for operation.

Operation:-

A right paramedian incision was made and a typical chronically inflamed appendix removed. Ovaries and uterus normal. Stomach and duodenum also apparently normal. Abdomen closed.

The patient made an uneventful recovery.

She reported $3\frac{1}{2}$ months later. She had returned to work and was feeling fitter than she had done for many years. There were no abdominal symptoms.

Many/

Many similar cases could be quoted of patients, who do not seem the least neurotic, yet complain of symptoms closely resembling gastric or duodenal ulcer who are permanently cured by the removal of an inflamed appendix. Cholecystitis or cholelithiasis often acts very similarly. Such cases are at least a biological indication of the dependence of gastric and duodenal symptoms and signs on irritation of the visceral (vagus) nerves.

The combination of organic disease of stomach, gall bladder and appendix is not infrequent (78) and occasionally symptoms pointing to the appendix only have been present for some years before the Gastric Ulcer or Duodenal Ulcer apparently developed. This may be an indication that irritation in the appendix actually caused the gastric disease, but we have no real proof of it and all lesions may quite as well be due to a common source, or even a streptococcal infection. (78)

Sixteen cases of chronic appendicitis with symptomatology like that of Gastric Ulcer or Duodenal Ulcer were published by Thompson of St. Louis. Nearly all showed hyperchlorhydria; in fact the average free acid in the stomach one hour after a test meal was 50 cc. decinormal Hydrochloric acid per 100 cc. of gastric contents while the total acidity/

acidity was 67 cc.

All came to operation, all had chronic appendicitis and had the appendix removed. All were very much better and most completely cured. In some who were tested, the gastric acidity had been lowered.(125)

So much for reflex causes of gastric disorders. We also know that organic disease of the brain may produce even chronic ulceration of stomach or duodenum.(15)

It remains to show that functional disorder of the autonomic system may be acquired through life apart from or in addition to, a vagotonic tendency.

(b) Tobacco Smoking.

One other cause of variation in the autonomic balance is the smoking of tobacco. Quite apart from the direct irritant effect of swallowed saliva containing dissolved bitter substances from the tobacco, nicotine especially from the smoke of a pipe or cigar is absorbed from mouth, stomach and lungs in quite considerable proportion. Nicotine is definitely a parasympatheticomimetic drug and produces increase in the motility and acid secretion of the stomach. There is therefore a very good reason why the physicians always advise patients with ulcerative tendencies to stop smoking.

(c) Anxiety Factors.

Amongst physicians it is a well recognised fact that recurrence of an ulcer is frequently associated with a period of anxiety or mental stress and the anxiety factor has been gaining much favour as a cause of gastro-duodenal ulceration in the past year or so. (126) (127) (128) (129) (130)

The primary response of the human organism to fear or anxiety, in common with the lower animals, is a mass sympathetic discharge making him prepared for "fight or flight". This includes cessation of motility of the alimentary tract with constriction of its vessels.

However, there is evidence to show that, in the human being, with continued repetition of anxiety stimuli, the stomach ceases to be influenced by psychic inhibitory factors, in other words the sympathetic side of gastric (and other alimentary) innervation fails to react, thus leaving the vagal complement to produce its action alone, with the result that after a time the usual reaction to anxiety and fear is in the direction of hypermotility and hypersecretion.

An illustration of this can be had in those unfortunate people who before an examination or important/

important interview or other like harrowing performance, are greatly afflicted by cold sweats, borborygmi, watery diarrhoea and frequency of micturition. Data on a more scientific basis may be obtained from the work of Todd (131) whose studies on the "behaviour pattern" of the stomachs of medical students from their first year onwards is most enlightening. He found that whatever the original response to anxiety factors was, the ultimate one was instability in the direction of hypermotility. He states that "hyperactivity of the stomach is always present in the anxiety complex and in patients consciously or subconsciously nervous but not afraid."

In some rare cases acute mental distress is followed by severe epigastric pain. In two such cases opportunity has been obtained of making a radiological examination following strong emotional stimulation. In both instances five or six waves of peristalsis were observed passing over the stomach at the same time, ^{giving} a picture of a sock filled with golf balls. (132)

IX. PERSONAL EXPERIMENTS.

The newcomer to the particular line of research work involving animal experiment, and especially survival experiments must frequently find himself surrounded on all sides by difficulties of which the solutions were by no means apparent.

One can learn a certain amount regarding experimental methods from the published reports of the works of others, but in these the descriptions of technique are usually conspicuous only by their absence, or alternatively are so scanty as to be of little value.

Secondly, one may assist and study at first hand the methods of one already experienced in the art of experiment and thereby gain invaluable information. The number of such men, however, who have both time and opportunity thus to teach novices is very limited, the which is to be regretted.

Lastly, one learns in the hard school of personal experience, from one's failures and from one's successes - a slow, trying, but withal, necessary procedure.

So the following pages are taken up with descriptions of some methods I have used, some of the difficulties which have presented themselves and in general an account of my endeavours to explore further the/

the cause of gastro-duodenal ulceration by means of experimental surgery.

From the observation of patients suffering from gastric or duodenal ulceration and from previous experimental evidence set down in the earlier part of this thesis, I have deduced that the two great factors in the causation of gastro-duodenal disease are the gastric secretion, in particular a raised Hydrochloric acid content and, nerve influences, in particular, a state of vagal hyperactivity. The objects of my research are thus:-

- (1) to produce a state of vagotonia or vagal hyperactivity in the stomach and
- (2) to examine the effect of that state on the gastric secretion;
- (3) to produce chronic gastric or duodenal ulceration by a method which imitates the apparent causative factors in man, that is to say by causing a state of vagal overaction with hyperchlorhydria to exist in the stomach of an experimental animal. Should this be found possible, then I think a very definite advance would have been made toward the ultimate solution of the problem of gastric and duodenal ulceration in man.

The Choice of Animal.

The cat was the animal chosen for the experiments because:-

- (1) in the anatomical arrangements of the stomach, in particular the distribution of the gastric nerves, it closely resembles man. I have checked this by dissections, but the fact has also been noted by others (19).
 - (2) Its gastric physiology is similar too. Also, one cannot fail to be struck by the manner in which the cat eats its food - a minimum of chewing and much bolting - so like the pre-ulcerous habits of man!
 - (3) The cat is available in reasonable numbers at a reasonable cost.
 - (4) Its organs and nerves are large enough to be submitted to the usual surgical operations.
-

THE ESTIMATION OF GASTRIC ACIDITY.

The preliminary experiments were directed towards the discovery of the most suitable method of estimating gastric acidity.

In the evolution of a method for this, the following conditions are desirable.

1. The animal must not be frightened or disturbed at the time of the withdrawal of gastric contents.
2. It must be in good health.
3. The normal continuity and motility of the alimentary tract must be interfered with to a minimum.
4. The method adopted should be as similar as possible to the clinical methods in common use, the Ewald Test Breakfast or the Rehfuess Fractional Test Meal.

Complete meeting of these conditions of course was not found possible, and some compromises had to be made as is not unnatural considering the human ability of co-operation in most cases, on the one hand, and the lack of that ability in the cat, on the other hand.

Gastrostomy with Tube.

The value of a simple gastrostomy in the withdrawal of gastric contents was first tried, thus following in the footsteps of that pioneer of gastrology, Beaumont.

Pre-operative Treatment.

(For gastrostomy and all other subsequent operations).

The animal is starved for at least 12 to 18 hours. Light open ether anaesthesia is then induced and the fur over the abdominal and lower chest wall clipped and shaved. Tinctura iodi mitis is applied and when dry, washed off with spirit.

The Operation.

Sterile towels are arranged in the usual manner to cover up all areas of the body except the small part of the abdominal wall where the incision is to be made.

A left paramedial incision is used, about $1\frac{1}{2}$ " long, the upper end of which is $\frac{1}{2}$ an inch below the costal margin. The skin only is incised with the first sweep of the knife, and spirit applied to the raw skin edges. Obvious vessels (there are sometimes two or three quite sizeable veins) are caught, divided between/

between forceps, and tied. The muscle is now cut, and side towels placed in position over the skin. The peritoneum is picked up in forceps, incised, and slit up with scissors.

The liver or the stomach, or both present in the wound. The liver is displaced upwards under the costal margin and the stomach gripped between finger and thumb and pulled out of the wound. A relatively bloodless part of the wall is chosen and two linen purse-string sutures inserted, one outside the other, but not tied. The stomach wall within the area surrounded by the sutures is incised and a soft rubber tube with both terminal and lateral openings inserted into the lumen. Soiling of the peritoneum is minimal if the animal has been starved, but further precautions are also taken, swabs being placed round the area of stomach exposed and suction apparatus being available to carry away any stomach contents. The purse-string sutures are tightened and tied, the stomach wall and tube being invaginated. Two stay sutures are placed through peritoneum and the wall of the tube.

The abdominal wound is now closed in layers -

1. Peritoneum and muscle together, with a mattress suture, leaving a gap for the tube. The stay sutures are tied to the muscle at each side of the gap, care being taken to choose a position for/

for the exit point so that the tube lies in the stomach without tension or bending.

2. The skin is sutured, the edges being carefully everted, using interrupted stitches. One stitch is put through tube wall and skin. The tube is cut $1\frac{1}{2}$ " from the surface and a clip applied to close its lumen.

Post-operative Results and Treatment.

All the animals recovered from the operation very quickly and remained well for 4 days or so. After this period various complications affecting either the animals' health or the functional result of the operation ensued.

1. The tube loosened and came out, and it was found very difficult or impossible to replace the tube or even to pass a smaller one in order to withdraw stomach contents. The gastrostomy opening gradually closed up.
2. The wound went septic. The causes of this were explored. Contamination at operation was considered, but this source was thought to be unlikely because an aseptic technique as for human operations was strictly adhered to. Furthermore, peritonitis was not present at autopsy/

autopsy except in one case where pus had formed under the skin and burst through the internal suture line to form a subphrenic abscess.

3. Leakage of gastric juice along the outside of the tube was probably a factor. Some digestion of the tissue with diminished resistance would occur in those cases, thus making infection from without all the simpler. This type of infection appeared to be operative in most cases.

Methods to counteract post-operative sepsis.

1. No matter how firmly a bandage and dressing was applied short of embarrassing the respiration, only a very short time elapsed before it had come undone. This was therefore useless.
2. First dressings were then sutured to the skin in 6 to 8 places, at the end of the operation. It is surprizing however, how mobile a cat's abdominal skin is, and in a matter of 24 hours, the animal had managed to pick away at least one corner, with the result that sawdust and other foreign matter had collected between dressing and wound.
3. Smearing substances over the wound area and repeating this daily was next tried and found to be the most successful method. The substances tried/

tried were sterile vaseline, collodion and zinc oxide paste.

The zinc oxide was the best and even minimised considerably the excoriation following upon gastrostomy without tube, or upon a gastric pouch with skin opening. Abdominal wounds without fistula did well without any application whatsoever.

The Method of Withdrawing Specimens.

A 30 cc. Syringe is attached to the gastrostomy tube and the clip released. Suction is applied and stomach contents withdrawn at varying intervals after a test meal as will be described later.

Difficulties.

As previously noted it was difficult to keep the tube in position. In fact, out of the 8 experiments of this type tried in no case was the tube in place without interference at the end of two weeks. In some cases, attempt was made to replace a tube that had come adrift but the opening contracted so much that this was found impossible.

In several of the autopsies, slight congestion of the gastric mucosa in the region adjacent to the tube/

tube was noticed. It was considered that some irritation was taking place, and that this might falsify results. (Irritation of the gastric mucosa produces a secretion of mucus leading to lowered acidity).

In face of these happenings therefore this means of obtaining gastric juice was discontinued and search made for other methods.

Gastrostomy without Tube.

After the usual preparations the stomach was exposed through a left paramedial incision. The anterior wall of the stomach was then fixed with 2 stay sutures and a cut 2 cm. long made in a relatively bloodless part of it. The edges of the gap were fixed to the muscle and peritoneum of the abdominal incision, the rest of which was closed. Through and through interrupted sutures were used. The skin edges were stitched together above and below the gastrostomy opening.

Results:

The functional result was a considerable improvement on the gastrostomy with tube. The opening did not tend to close so much and a soft rubber catheter could be inserted and specimens withdrawn without an anaesthetic and without distressing the animal.

There was one great drawback however. The abdominal muscles round the mouth of the fistula by no means acted as a sphincter and very considerable leakage took place which it was impossible to control even by external bandages or sticking plaster. Excoriation and occasional sepsis occurred round the fistula in spite of zinc oxide paste applications. Much of the animals' food found its way out of the gastrostomy, and loss of weight was considerable.

4 such animals were prepared, 2 of which died and 2 of which were killed.

Other Methods of constructing Gastric Fistulae.

The insertion of a flanged silver tube with stopper used by Pavlov in his sham feeding experiments was not tried in cats.

A Janeway fistula is probably the most successful method but its construction may interfere to quite an extent with the nerve supply of the stomach, and since in my experiments the gastric fistula was only a preliminary to studying the effects of nerve stimulation, it was not of the same value as in other experiments.

There is an exceedingly ingenious method of making a non-leaking fistula (133) which consists of resecting a few centimetres of lower ileum complete with attached mesentery and blood vessels which act as a pedicle. The continuity of the ileum is restored by end to end anastomosis. The resected portion of ileum then is made to form a passage between the skin surface and the stomach to which it is joined by an end to side anastomosis, the direction of automatic peristalsis of the piece of ileum being from skin towards stomach. No leakage thus takes place, but a tube is easily passed through into the stomach when it/

it is wished to withdraw contents.

From the preceding remarks it will be seen that a gastric fistula is rather a troublesome way of collecting gastric juice in cats. The Janeway fistula would appear to be the most valuable and the least troublesome, and I refrained from its use only because of the interference with some of the gastric nerves that it entailed, an occurrence which I particularly wished to avoid.

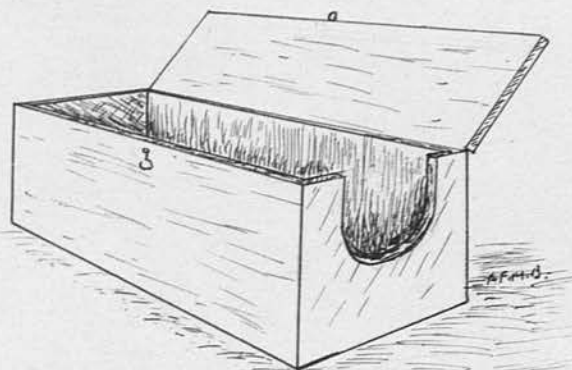
The Use of the Stomach Tube.

An imitation of the clinical method of carrying out a Test Meal was tried. There were several modifications which had to be made due to the animal's inability to co-operate in the test as most patients will. The object of the procedure was to withdraw gastric contents by stomach tube without the cat being frightened or upset.

First a cat-box was constructed. This is an oblong wooden box with hinged lid and catch, large enough to contain an average sized cat. A U-shaped piece is cut out of one of the ends starting from the upper edge. The measurements between the limbs of the U, and from the concavity to the closed lid of the box are each 3 inches. (See Fig. 18)

Once daily for some 3 days, each animal was taken out of its cage, and allowed to stand or sit in/

FIGURE 18 a.



CAT BOX.

FIGURE 18 b.

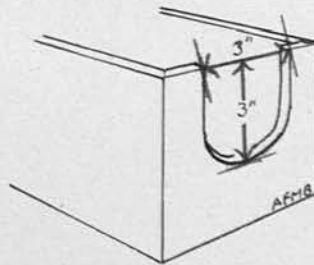
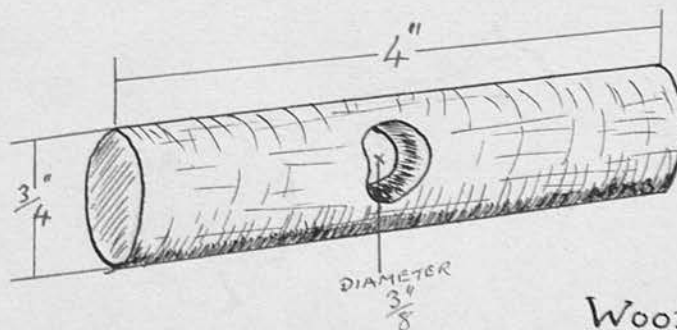


FIGURE 19.



WOODEN GAG.

in the box without the lid being closed. The cat was petted and some fish offered to it. It was allowed to remain in the box for 5 minutes. For the next day or so, the cat was again placed in the box for 5 minutes, the lid being closed this time, the neck projecting through the U-shaped aperture, which was of such a size that the head was too big to be withdrawn into the box, yet the neck was in no wise constricted. Usually after some 5 to 7 days, the animals showed no fear and seemed quite comfortable and at ease.

A cylinder of wood 4 to $4\frac{1}{2}$ " long and $\frac{1}{2}$ " to $\frac{3}{4}$ " in diameter was obtained and a hole of $\frac{3}{8}$ " diameter, bored diametrically through the cylinder (See Fig. 19). This piece of wood was placed up against the cat's teeth until it opened its mouth, when the wood was put between the teeth allowing the animal to bite on the wood. Tolerance was given to this procedure after some 5 to 10 days practice.

Now came the job of passing a stomach tube. The Rehfuß tube as used clinically of course was useless, and a soft rubber tube 15" long and of $\frac{3}{16}$ inch bore with an oblique terminal opening, and a lateral opening was made.

While an assistant held the wooden gag in position, the tube, well lubricated, was passed through the hole in the gag, and so to the stomach. The first 5 or 6 times this was done, the animal became very/

very excited and wriggled a great deal, so that the gag often slipped and the tube had to be hastily withdrawn to prevent the cat biting holes in it. But it was amazing how after a week or 10 days tolerance was established and the tube was allowed to remain 30 secs. to 1 minute without wriggling or apparent fear - a sufficient time to allow a sample of contents to be withdrawn. Immediately after removal of the tube the cat was quite friendly and often purred loudly, or ate with obvious relish the test meal which was given just after the fasting juice had been removed.

From 4 - 5 weeks from the commencement of the use of the cat box, the acid values began to be more constant and therefore of some use.

The Test Meal.

Quite a variety of different meals have been tried by various workers including plain water, 7% alcohol, meat, gruel etc. etc. In these experiments however, it was decided to use only a meal which the animal relished and would eat readily in its usual manner, because obviously any substances given by stomach tube only affect the stomach, the psychic and reflex secretion being cut out. Alcohol also was not considered in view of its peculiar action on the stomach mucosa.

After experiment 50 gms. approx. of finely mashed filleted/

filleted haddock or whiting was found to give the best results.

Another difficulty which dogged the whole series of experiments was that of withdrawing specimens even after the stomach tube had been successfully passed. Withdrawal was particularly difficult while the animal was fasting or during the first $1\frac{1}{2}$ hours of the test.

This was discovered to be due to several factors.

- (1) Small quantity of juice.
- (2) Presence of very viscid mucus much stickier than that observed in the human being.
- (3) The presence of foreign matter in the stomach such as sawdust and hairballs which were found frequently.

Attempted withdrawal of contents by the usual clinical method of attaching a syringe directly to the end of the stomach tube and drawing out the piston was so frequently attended by failure that a simple modification was introduced. The apparatus is seen in Fig. 20. It consists of a stomach tube leading to a small collecting bottle. From the bottle a lead is taken to a 30 cc. syringe with close fitting piston and 2-way attachment.

Small quantities of secretion could often be extracted by first injecting a few ccs. of air before applying suction.

Placing/

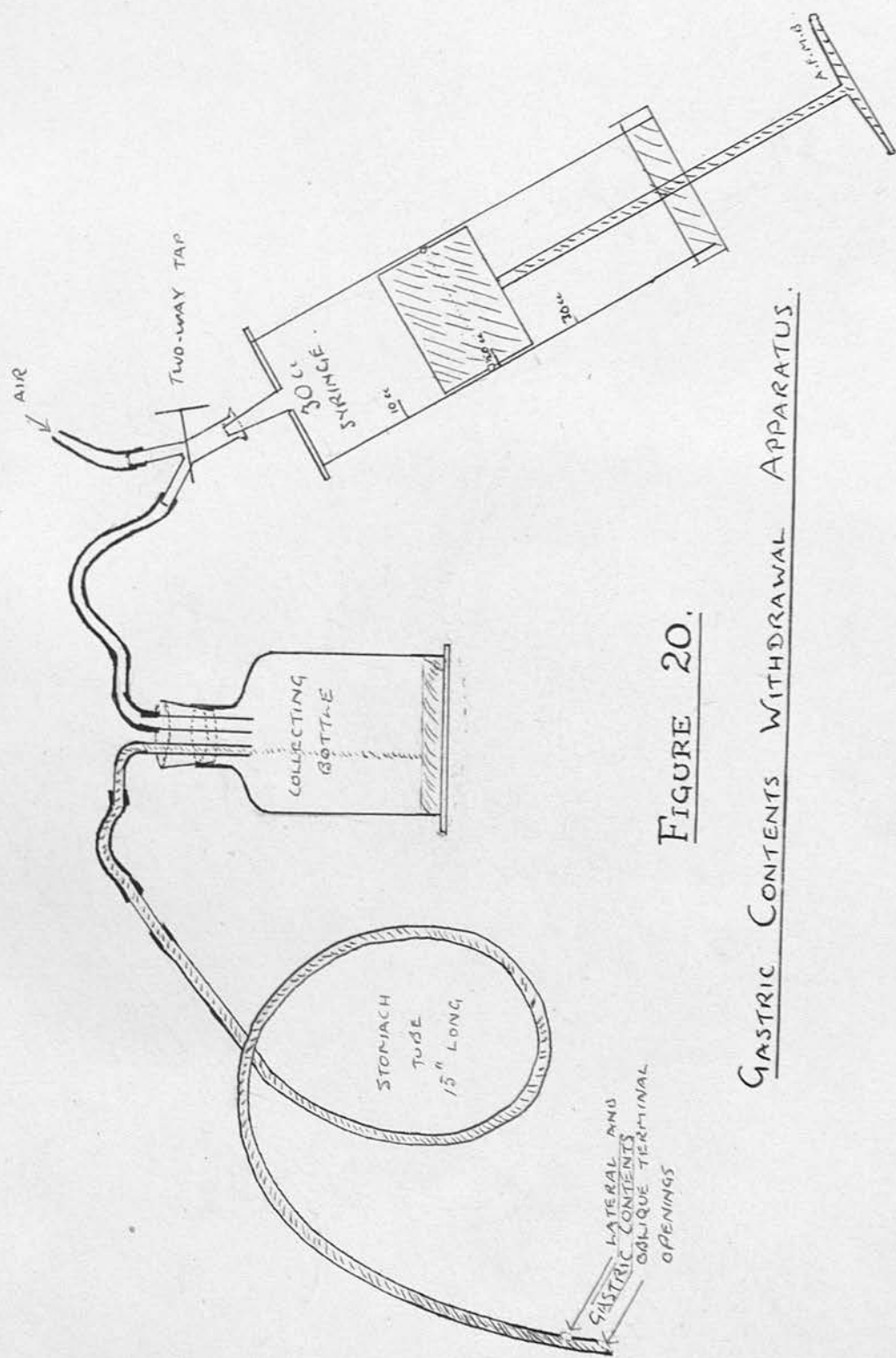


FIGURE 20.

GASTRIC CONTENTS WITHDRAWAL APPARATUS.

Placing the collecting bottle between the stomach tube and the syringe obviates the necessity of the viscid contents having to pass through the small bore of the syringe nozzle.

A considerable negative pressure could also be obtained in the collecting jar by manipulation of the 2-way connection (as in a Potaine's Aspirator), and this often served to clear the stomach tube of thick mucus without withdrawing the tube. Extraction of juice in this manner was about 50% successful. From $1\frac{3}{4}$ hours after the meal till the stomach was empty, withdrawal was easy since the contents of the stomach had become much more fluid.

Owing to the numerous difficulties met with, to the time consuming nature of the training of the animals, and to the most annoying habit of some of the cats to die of distemper or respiratory infection just when training was complete, only 8 experiments were done.

Gastric contents were withdrawn immediately before, and at varying periods after the meal. The contents were titrated with $\frac{N}{10}$ NaOH using Topfer's Reagent to indicate the end point for Free Acid and 0.1% Phenolphthalein for Total Acid.

The average normal curve obtained is shown in Fig. 21.

GASTRO-INTESTINAL ANALYSIS.

Name of Patient

Ward

Bed

I. FRACTIONAL TEST-MEAL. Date.

Fasting Juice.

Volume. / cc.

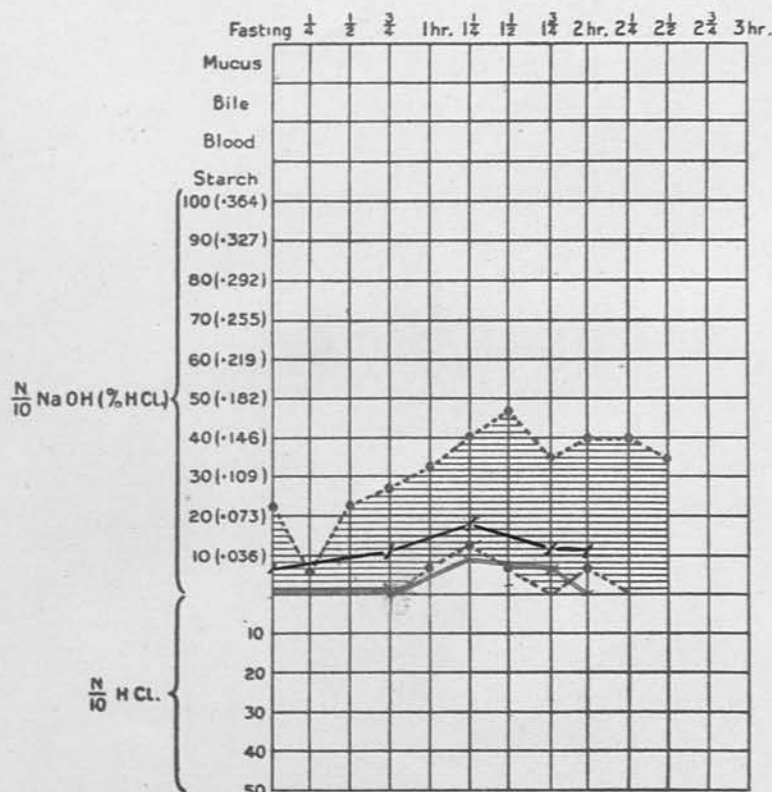
Cells.

One Hour Fraction.

Free HCl.

Active HCl.

Total Chloride.



The shaded area represents the limits for free HCl. in 80% of normal people, and average rate of emptying (2-2 1/2 hours).

RED represents free HCl.
BLACK represents total acidity.

Summary.

AVERAGE TEST MEAL ACID CURVE (CAT)

GASTRIC CONTENTS RECOVERED BY STOMACH TUBE.

2. FÆCES.

2. DIRECT VAGAL STIMULATION.

Having established a method of estimating gastric acidity I now proceeded to work out a method of stimulation of some part of the nervous system with the object of altering the acidity of the gastric juice in the direction of hyperchlorhydria. The obvious nerve to choose was the vagus. The optimum point of stimulation I considered was the left vagus nerve as low down in the neck as possible. This choice was arrived at largely by means of exclusion of other points in the nervous system.

From a general review of the literature it is obvious that it is through the parasympathetic nervous system that the secretion of acid is mainly controlled. Since the vagi form the parasympathetic supply of the stomach a suitable point on that nerve was sought.

Abdominal vagi:- This site was a possibility, but the nerves as they come through the diaphragm in the cat are rather short and difficult of access being tucked away up behind the costal margin. Further, it was desired to avoid any interference with the abdominal parietes. It appears that even cutting the anterior abdominal wall, without touching the stomach or doing anything else may have quite marked effects on the motility and action of the stomach.

Intrathoracic/

Intrathoracic vagi:- the operative and anaesthetic difficulties were too great at this site.

High Cervical and Intracranial Course:- Again the operative difficulties here are too great, at least for one unskilled in cerebral surgery. Also, any stimulation in this region above a certain small minimum amount causes great spasm of the glottis and serious respiratory embarrassment with frequent death from pneumonia subsequently.

Low Cervical region:- This was the point chosen. It was below the laryngeal nerve and missed some of the cardio-inhibitory fibres. It was realised of course, that stimulation at this point without section of the vagus nerve would produce impulses directed centrally as well as peripherally which might at first sight be thought to render the results of the experiments equivocal, but when one considers the type of person that suffers from hyperchlorhydria and/or gastric or duodenal ulceration, it will be seen that those patients also show general vagotonic manifestations such as slow pulse, low blood pressure, sweaty hands and feet, etc., which are of central origin: therefore, the additional central stimulation thus attained makes the comparison with human beings all the closer.

The left vagus nerve was chosen as experiments and dissections show that although some fibres from both/

both nerves ultimately end in the stomach, more seem to come from the left vagus than the right. Direct Electrical Stimulation of the left vagus nerve in the lower cervical region then, was deemed the most expedient method, so I designed, constructed and attached a single electrode to that nerve.

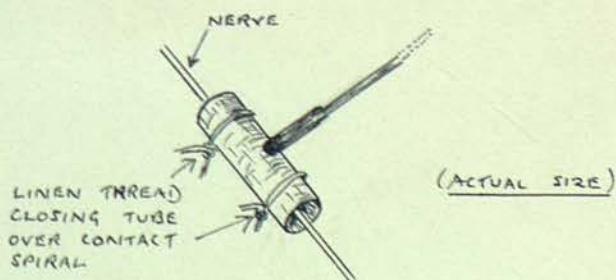
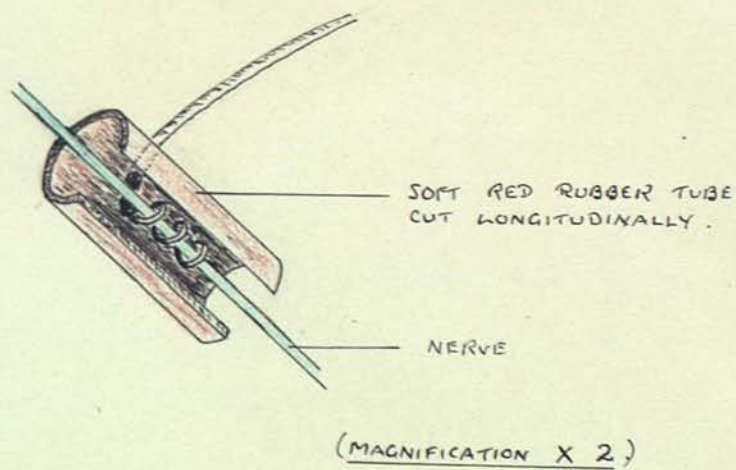
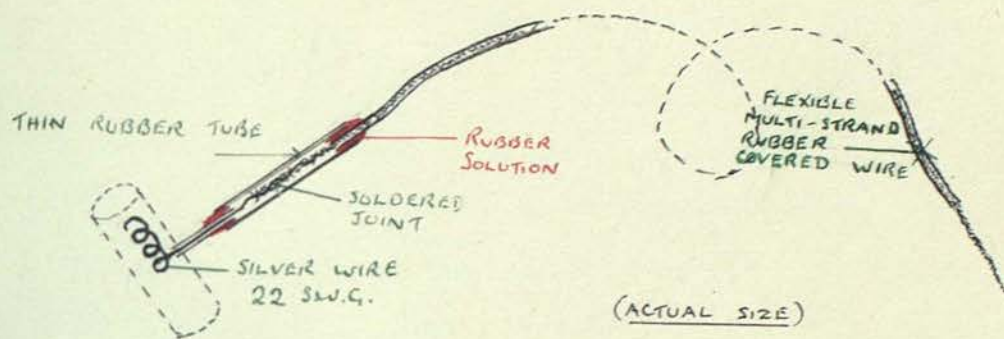
Construction of Electrode.

The contact piece was of fine gauge silver wire formed into a spiral of some 3 complete turns. One end of the wire was soldered to a multistrand flexible wire with rubber insulation. The joint was smeared with rubber solution and very thin tight fitting rubber tubing pulled over it and sealed down with more rubber solution, leaving only the spiral of silver wire exposed. To obtain insulation while the electrode was in situ, the contact piece was encased in a short piece of rubber tubing and this was arranged as in Fig. 22.

Thin rubber tubing of $\frac{3}{16}$ " bore was used. A piece $\frac{1}{2}$ " long was cut off and slit up longitudinally. Diametrically opposite the cut, towards one end, a small hole was made and the electrode pulled through the contact spiral being bent to an angle of 90° so that it lay without strain in the lumen of the rubber tube.

The/

FIGURE 22.



The whole was sterilized by immersion in lysol for 48 hours and storing thereafter in spirit.

Implantation of the Electrode.

The animal's neck is shaved and under ether anaesthesia after the usual preoperative, and with full aseptic precautions, a small incision is made in the back of the neck. Artery forceps are inserted and worked forward through the superficial tissues of the left side of the neck till the points reach to within 1" of the midline, where they are closed and left.

The animal is now turned on its back and an incision made in the lower part of the neck parallel and just medial to the superficial jugular vein which can be seen through the skin. The lateral skin edge and vein are retracted laterally and the underlying muscle cleared and cut in the line of the skin incision. The muscle edges are retracted and the carotid sheath defined as it lies just lateral to the trachea. This sheath is incised for the distance of 1" to $1\frac{1}{4}$ " and the vago-sympathetic nerve isolated. With great care the very thin sheath binding the two nerves together is incised and the vagus which is the larger trunk separated from the cervical sympathetic by slow careful dissection with two needles gradually insinuated into/

into the small division between them.

The electrode is next produced and rubber sheath held back while the spiral is twisted on to the vagus. When the nerve lies freely within the spiral, the rubber tube is slipped over the whole (which is easily done because of the longitudinal cut already made in it). A fine suture is passed round each end of the tube and tied, in order to preclude the possibility of the nerve or electrode slipping out. (Fig. 22)

The forceps which had been inserted from the back of the neck at the start of the operation are now pushed forwards and steadied. The points projecting through the lateral leaf of the muscle. A small cut is made over the forceps which are pushed through the muscle. The end of the flexible lead is caught and drawn to the outside so that the electrode lies comfortably without tension. The muscle is drawn together with 3 interrupted sutures and if the incision has been made as already described the sheathed electrode will be lying under a shelf of uncut muscle and not directly under the suture line. The skin incision is stitched and a collodion dressing applied. The flexible lead is attached to the skin edge at the back of the neck, and a small collodion dressing applied to it also. The lead is wound into the form of a small coil and left free till required on the back of the neck, where the animal cannot reach it.

The/

The wounds as a rule healed well and sepsis was not a serious trouble.

I now had cats, the nature of whose response to a test meal was known and which had electrical leads attached to the left vagus nerves. Electrical stimulation of that nerve was now proceeded with.

Direct Electrical Stimulation of the Vagus.

A large lead electrode such as is usually employed in the application of diathermy was fixed to the body or tail of the cat over a pad of lint soaked in normal saline, the lead being brought out under the lid of the cat box. This lead and the one fixed to the vagus which appeared through the neck hole of the box were taken to the appropriate terminals of a Pantostat, an instrument which works off the 230 volt mains and supplies different types of current at a lower potential, e.g. galvanic cautery, light, sinus, etc.

The sinus current of 50 cycles per second was used.

The cat was sitting quietly in the box and the instrument started up. A diaphragm stethoscope had been fixed against the chest wall with sticking plaster.

The rheostat controlling the sinus leads was very gently moved and as the current increased the heart rate gradually decreased. When the rate had been halved/

halved no further adjustment was made but the current allowed to flow for 10 - 15 minutes.

The animal retched and wriggled a little at the beginning but in a very few seconds settled down and did not appear to be upset.

Results.

Out of the 8 cats which had been trained and had leads implanted, 2 died without obvious cause and at post-mortem general congestion of the alimentary tract was the only apparent abnormality.

2 died of respiratory infection with signs of bronchopneumonia at post-mortem.

In 2 the implanted leads were found on the floor of the cage.

In the first four cases at post-mortem the electrode was lying in a small cavity, filled with opalescent fluid, the walls of which were new fibrous tissue. The fluid was mainly composed of fibrin and lymphocytes and appeared sterile. The electrical function of the electrode however, did not seem to be interfered with since even small stimuli produced an immediate fall in the heart rate.

Only 2 prepared animals now remained. In one after 3 days stimulation the neck wound opened up (probably due to some pressure in the cat box) and the fluid in the electrode cyst described above escaped/

escaped. Two days later the electrode was found lying in the animal's cage.

In the remaining cat after 2 days stimulation, slight traction was inadvertently put on the electrode lead in disconnecting it from the Pantostat and it also came adrift.

In these 2 animals however, test meals as already described performed immediately after the 15 minutes stimulation showed the acid curve to be slightly increased. (See Figs. 23 to 26).

Summary of Results: Series I.

(Direct Stimulation of Vagus.)

- Cat No.1. Electrode came adrift.
- " No.2. Died without apparent adequate cause.
- " No.3. As No.2.
- " No.4. Died of Respiratory infection.
- " No.5. Test Meal after vagal stimulation showed increased percentage of acid above the highest obtained before stimulation. In particular there was free Hydrochloric acid in the "fasting juice".
- " No.6. Died of Respiratory infection.
- " No.7. Same as No.5.
- " No.8. Electrode came adrift.

These/

GASTRO-INTESTINAL ANALYSIS.

Name of Patient

CAT 5

Ward

Bed

I. FRACTIONAL TEST-MEAL.

Date.

Fasting Juice.

Volume.

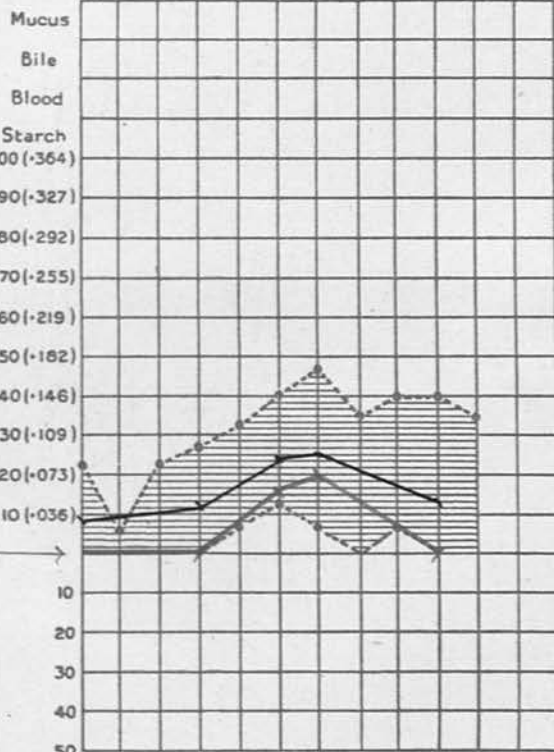
 $\frac{1}{4}$ cc.

Cells.

FASTING JUICE

VOLUME LOW
MUCH MUCUS

NO FREE HCl.

 $\frac{N}{10}$ NaOH (% HCl) $\frac{N}{10}$ HCl.Fasting $\frac{1}{4}$ $\frac{1}{2}$ $\frac{3}{4}$ 1 hr. $1\frac{1}{4}$ $1\frac{1}{2}$ $1\frac{3}{4}$ 2 hr. $2\frac{1}{4}$ $2\frac{1}{2}$ $2\frac{3}{4}$ 3 hr.

One Hour Fraction.

Free HCl.

20

Active HCl.

Total Chloride.

The shaded area represents the limits for free HCl. in 80% of normal people, and average rate of emptying (2-2½ hours).

RED represents free HCl.

BLACK represents total acidity.

{ HIGHEST "NORMAL" CURVE OBTAINED.

FREE HCl = 20cc $\frac{N}{10}$ acid. (1½ HOUR FRACTION)

Summary.

No. 5.

2. FÆCES.

GASTRO-INTESTINAL ANALYSIS.

Name of Patient

CAT 5

Ward

Bed

1. FRACTIONAL TEST-MEAL. Date.

Fasting Juice.

Volume. $5\frac{1}{2}$ cc.

Cells.

FASTING JUICE

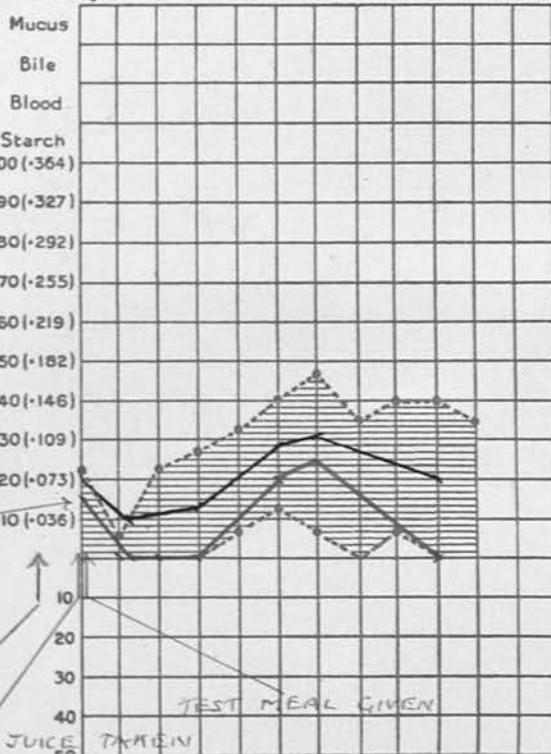
VOLUME INCREASED

FREE ACID PRESENT

 $\frac{N}{10}$ NaOH (% HCl) $\frac{N}{10}$ HCl.VAGAL STIMULATION
(15 MINUTES)

FASTING JUICE

TAKEN IN

Fasting $\frac{1}{4}$ $\frac{1}{2}$ $\frac{3}{4}$ 1 hr. $1\frac{1}{4}$ $1\frac{1}{2}$ $1\frac{3}{4}$ 2 hr. $2\frac{1}{4}$ $2\frac{1}{2}$ $2\frac{3}{4}$ 3 hr.and $\frac{1}{2}$
One Hour Fraction.

Free HCl. 25

Active HCl.

Total Chloride.

The shaded area represents the limits for free HCl. in 80% of normal people, and average rate of emptying (2-2½ hours).

RED represents free HCl.

BLACK represents total acidity.

AFTER VAGAL STIMULATION.

FREE HCl = $25 \text{ cc } \frac{N}{10} \text{ ACID.}$

COMPARE WITH

HIGHEST "NORMAL" = $20 \text{ cc } \frac{N}{10} \text{ ACID.}$ (BOTH $1\frac{1}{2}$ HOUR FRACTION)

Summary.

No. 5.

2. FÆCES.

GASTRO-INTESTINAL ANALYSIS.

Name of Patient

CAT 7.

Ward

Bed

1. FRACTIONAL TEST-MEAL.

Date.

Fasting Juice.

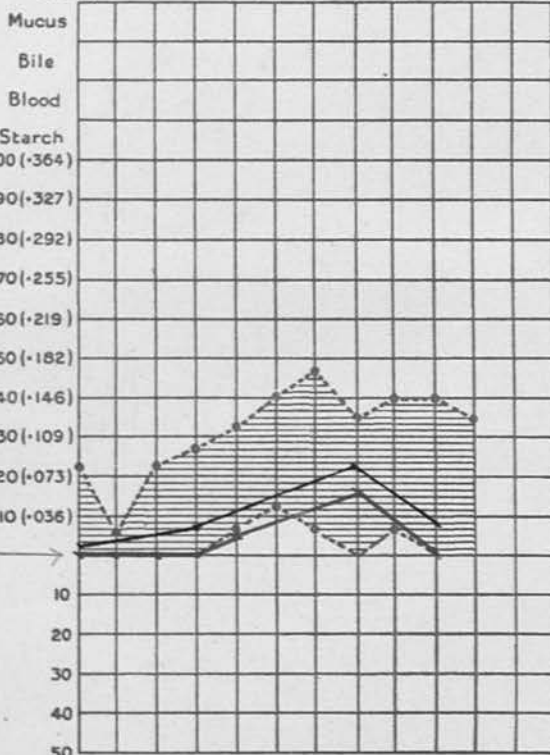
Volume. $\frac{3}{4}$ cc.

Cells.

FASTING JUICE

VOLUME LOW
MUCH MUCUS

NO FREE ACID.

 $\frac{N}{10}$ NaOH (% HCl) $\frac{N}{10}$ HCl.Fasting $\frac{1}{4}$ $\frac{1}{2}$ $\frac{3}{4}$ 1hr. $1\frac{1}{4}$ $1\frac{1}{2}$ $1\frac{3}{4}$ 2hr. $2\frac{1}{4}$ $2\frac{1}{2}$ $2\frac{3}{4}$ 3hr.

One Hour Fraction.

Free HCl.

Active HCl.

Total Chloride.

The shaded area represents the limits for free HCl. in 80% of normal people, and average rate of emptying (2-2½ hours).

RED represents free HCl.

BLACK represents total acidity.

HIGHEST "NORMAL" CURVE OBTAINED.
FREE HCl = 15 cc $\frac{N}{10}$ ACID IN $1\frac{3}{4}$ HOUR SPECIMEN.

Summary.

No. 7.

2. FÆCES.

GASTRO-INTESTINAL ANALYSIS.

Name of Patient

CAT 7.

Ward

Bed

1. FRACTIONAL TEST-MEAL.

Date.

Fasting Juice.

Volume. $3\frac{1}{2}$ cc.

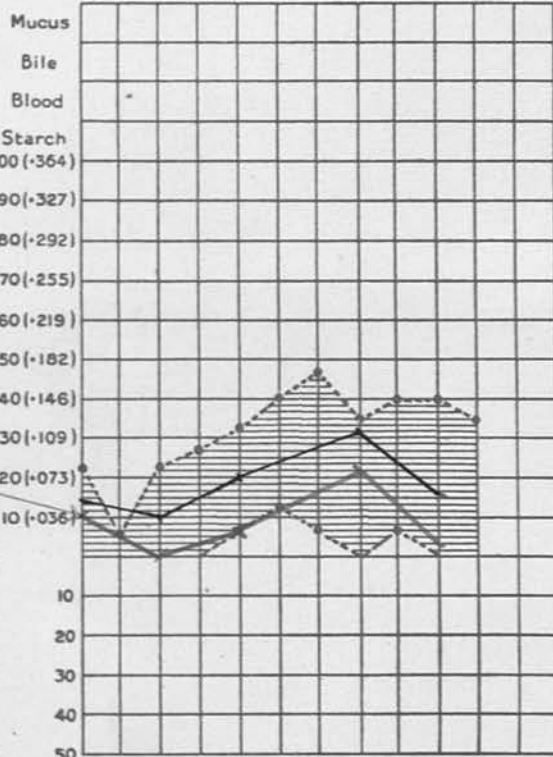
Cells.

FASTING JUICE

 $\frac{N}{10}$ NaOH (% HCl)

GREATER VOLUME

FREE ACID PRESENT

 $\frac{N}{10}$ HCl.Fasting $\frac{1}{4}$ $\frac{1}{2}$ $\frac{3}{4}$ 1hr. $1\frac{1}{4}$ $1\frac{1}{2}$ $1\frac{3}{4}$ 2hr. $2\frac{1}{4}$ $2\frac{1}{2}$ $2\frac{3}{4}$ 3hr.

One Hour Fraction.

Free HCl.

Active HCl.

Total Chloride.

The shaded area represents the limits for free HCl. in 80% of normal people, and average rate of emptying (2-2 $\frac{1}{4}$ hours).

RED represents free HCl.

BLACK represents total acidity.

Summary.

No. 7.

AFTER VAGAL STIMULATION

FREE HCl = 22 cc $\frac{N}{10}$ ACID.HIGHEST "NORMAL" = 15 cc $\frac{N}{10}$ ACID.

FREE HCl

(BOTH IN $1\frac{3}{4}$ HOUR SAMPLE.

2. FÆCES.

These experiments were of course only of a preliminary nature but are probably a further indication that vagus stimulation does produce a raised secretion of acid in the stomach.

The technical difficulties however were so hard to solve satisfactorily, the training methods so time consuming and tedious, and the results in the end so apparently uncertain, and the rise of Hydrochloric acid obtained during the meal so small that the chance of ulcer production (which was the original hope of the experiments) so remote, that further experiments were not carried out.

Also, just at the end of these experiments I found an article by Ettinger, Hall and Banting, (134) in the Canadian Medical Association Journal which contained reports of experiments performed on very similar lines to my own, but much more fully carried out (for a different object however).

Accounts of full post-mortem examinations on animals subjected to vagal stimulation for periods of 100 to 300 hours are given. Besides the accounts of the condition of the coronary arteries which was the main issue of the experiments it is stated that no chronic ulcers were noted. "Coffee ground" vomit and bloody diarrhoea were frequently seen: also general congestion of the alimentary tract. Capillary bleeding/

bleeding was presumed to be the cause of this finding.

Stimulation of the Vagus by Induction.

Concurrently with these experiments I made a few other tentative trials of another method. This was the method of more continuous nerve stimulation by implantation of a small secondary coil the ends of which are placed on the vagus nerve.

The whole animal is put in a special cage which is wound round with many turns of wire forming the primary coil of the apparatus. The animal may be left in the cage for several hours daily while the current is circulating. The secondary coil within the animal is therefore in the induction field of the primary. The current is picked up and applied to the nerve trunk in the animal. The method was originally tried by Lubeck. (135)

Other experimenters have applied the secondary coil electrode to the cerebral motor cortex and obtained epileptic attacks during stimulation in the cage.

Mr W.A.D. Adamson has attached the secondary coil to the nerves to the suprarenal gland, a previous denervation of the eyeball having been done. When the animal was placed in the cage and the primary current started, dilatation of the pupil followed, presumably due to release of adrenalin from stimulation of the suprarenal nerves. (136)

My/

My experiments were again carried out in cats for reasons previously put forth.

The left vagus nerve was exposed in the lower cervical region as also previously described, but a larger skin incision was made. By blunt dissection a cavity was made in the loose tissues of the back of the neck, and the coil buried here, its end electrodes being placed on the vagus trunk.

I found that the cats persisted in rubbing their necks against the bars of their cages and the coil ulcerated through the intact skin although the operation wound healed up well. Infection soon supervened and the animals had to be sacrificed.

A much more successful method was to implant the coil in the loose tissue of the abdominal wall and bring a lead up through a subcutaneous tunnel over the chest. This performance however is liable to be complicated by sepsis in cats.

When the experiments of direct vagal stimulation through the implanted electrode fell through, it was thought exceedingly likely that the necessarily much weaker current applied to the nerve by the secondary coil would have even less chance of producing ulcer, and so these experiments were also discontinued.

In the article by Ettinger, Hall and Banting already/

already referred to, negative results of this method of stimulation are recorded. (134)

It is interesting to note this example of how a very attractive and well designed method theoretically proves to be so disappointing in practice.

3. EXPERIMENTS ON RELATIVE OVERACTION
 OF THE VAGUS NERVES.

Working from my deductions that the main factors in ulcer production were vagal overaction and the contact of the gastric mucosa with a high concentration of Hydrochloric acid over considerable periods, I tried to produce these two conditions in the cat, and note the result.

Since the technical difficulties in the production of vagal overaction by direct stimulation had proved to be so great, the indirect method of inducing a sympathetic paralysis of the stomach by section of the splanchnic nerves, and a consequent relative vagal effect was selected as the method of choice.
(34) (137) (Also see page 67.).

Although splanchnic section caused an increase of acid in the stomachs of cats, the rise was not very great, neutralization and dilution by means of food and extra-gastric secretions still occurring. So another manoeuvre was added to splanchnic section - the construction of a stomach pouch which had an intact vagal supply yet contained no food.

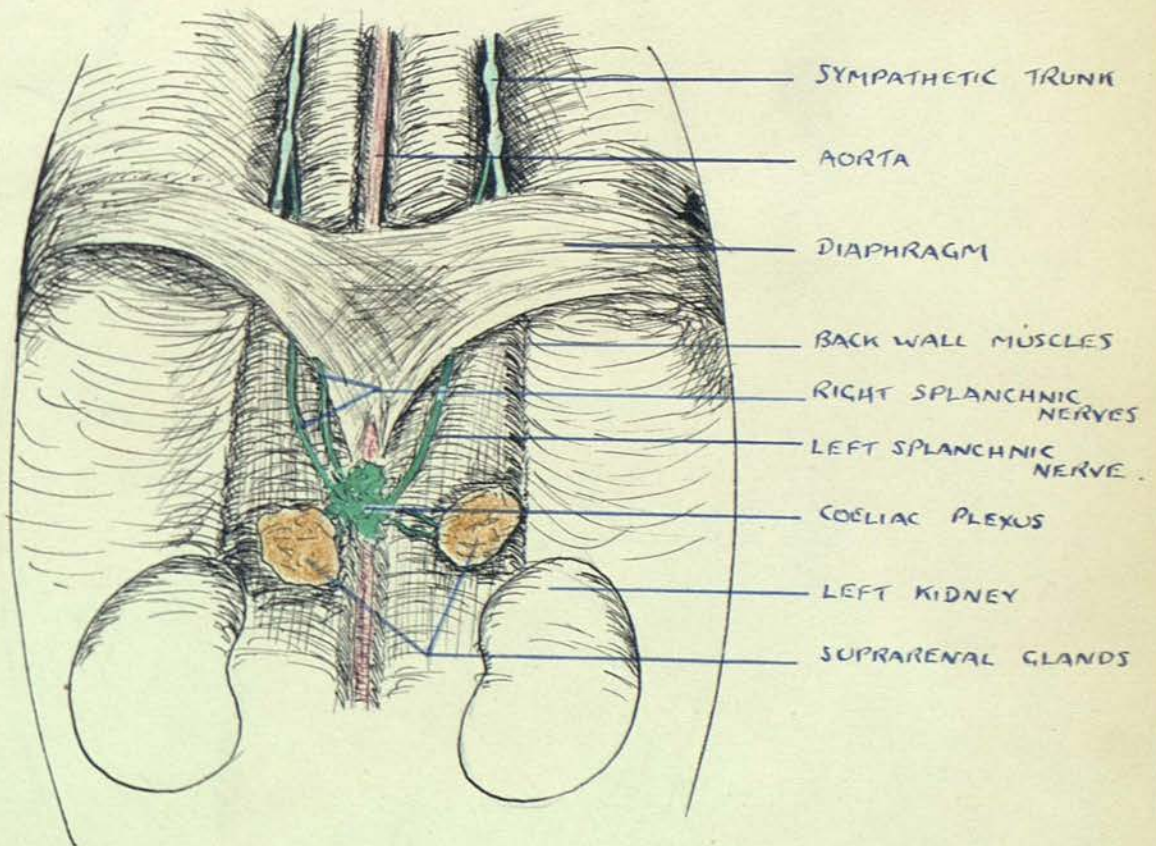
The complete operation was latterly done in two stages: first the bilateral splanchnic section (after which no ulcer developed) then about 3 weeks later the/

the gastric pouch with its nerve supply was isolated. Done in one stage, 3 cats out of 6 died within 3 days of the operation. On the other hand the immediate mortality after the two stage operation was very low.

To cut all and only the adrenergic nerves to the stomach is a technical impossibility because the actual terminal nerves which supply the stomach are very small and run in close company with vagal fibres. Nevertheless only a negligible number of sympathetic fibres reach the stomach, the central connections of which do not pass in the splanchnic nerves. (36) (37) (38) (105) Cutting a piece out of each splanchnic nerve just as it emerges through the diaphragm and before it enters the coeliac ganglion gives an efficient sympathetic denervation of the stomach. It leaves vagal fibres intact, it is a reasonably simple operation to perform, and the animals stand it well. (Fig. 27).

(In the descriptions that follow the words "above", "superior", "inferior" etc., are given their meanings as in anatomical terminology applied to the human being. Thus below = caudal)

FIGURE 27.



A DISSECTION SKETCH TO SHOW
RIGHT AND LEFT SPLANCHNIC NERVES
(CAT)

Stage I. Splanchnic Section.

After the usual preoperative measures and with all aseptic precautions, the cat being under open ether anaesthesia, a high right paramedian (or right lateral) incision is made care being taken not to go too deep as the liver lies very superficially and can easily be injured.

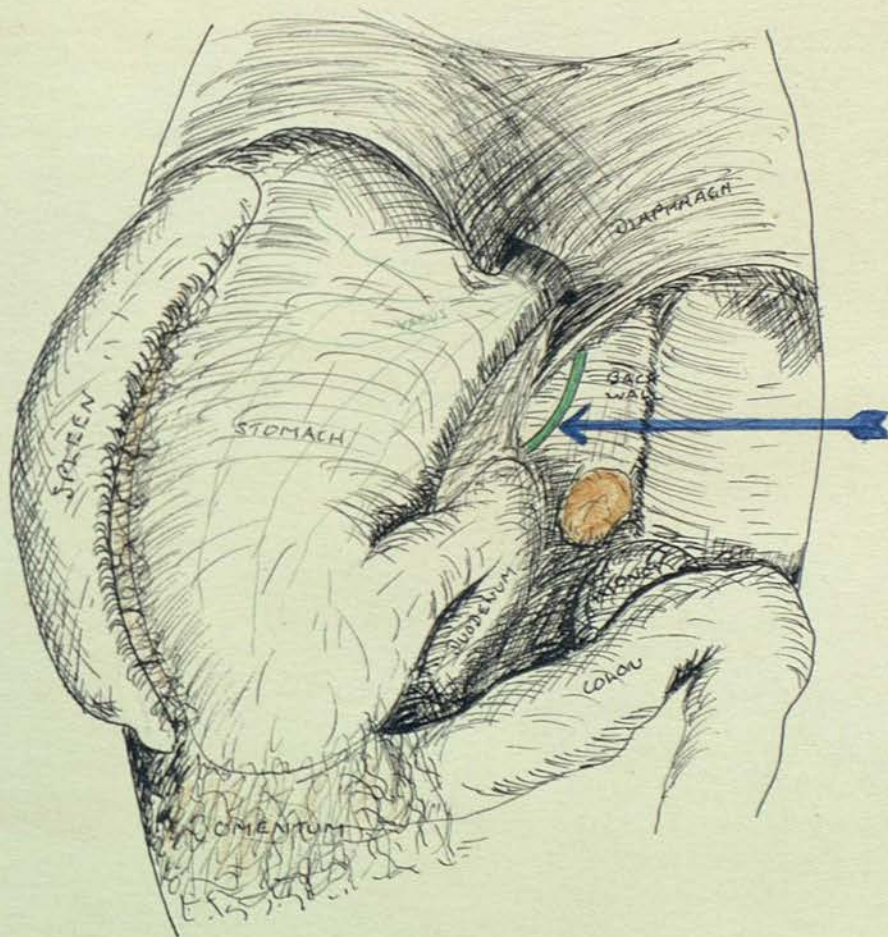
The left splanchnic nerve is first sought. The stomach and spleen are withdrawn from the wound and swung over to the animal's right. They are wrapped in gauze wrung out of warm normal saline. This manoeuvre usually brings the left suprarenal gland into sight as it lies behind the peritoneum on the back wall of the abdomen. If it is not seen the gentle use of a retractor, or the light packing away of the neighbouring viscera serve quickly to bring it into view. The gland is about the size of a split pea and its bright yellow colour makes it quite unmistakable.

The area for about $\frac{1}{2}$ an inch above the gland is relatively bloodless, and blunt dissection, with a pair of fine curved artery forceps, with perhaps the occasional touch of the knife, of the extraperitoneal fat and areolar tissue exposes a crus of the diaphragm and the muscles of the back wall. Emerging from the substance/

substance of this crus or immediately laterally, a fine but definite nerve is seen travelling medially and downwards towards the aorta which can be felt beating under the finger. (Fig. 28) This is the left splanchnic nerve; it is the only nerve with similar situation and course and is easily found. It is gripped with one pair of fine artery forceps as far medially as possible, and with a similar pair just as it leaves the diaphragm. It is cut close to each forceps and a piece of nerve $\frac{1}{4}$ " to $\frac{1}{3}$ " long is thus resected. The forceps at the diaphragmatic end are removed allowing the central end of the nerve to retract into the diaphragm or thorax. The forceps at the coeliac end are allowed to remain clamped on the cut nerve as they provide a useful indication of the less obvious right splanchnic roots. Any bleeding points are caught and tied, or haemorrhage controlled by pressure through a slightly damp swab. If slight bleeding takes place before the nerve has been isolated, a useful way of clearing the field of vision is to apply a fine suction nozzle to a small piece of damp cotton wool placed over the bleeding point. Haemostasis is rapidly obtained by this method when the bleeding is scanty.

Attention is now directed to the right splanchnic nerve or nerves. The stomach and spleen which have already/

FIGURE 28.



OPERATIVE EXPOSURE OF LEFT
SPLANCHNIC NERVE — STOMACH
AND DUODENUM SWUNG TO RIGHT

already been withdrawn from the abdominal cavity are wrapped in fresh gauze saturated with warm normal saline and swung over to the animal's left. Light traction is put on the stomach and duodenum and their peritoneal attachments followed down to the back wall. A retractor with slightly curved blunt end is placed here, holding stomach and duodenum back.

A lobe of the liver which descends in the mid-line or just to its right in this region is now gently turned up and its portal vein defined. Blunt dissection as described for the left nerve is now proceeded with in the space between the portal vein and the attachment of duodenum to the back wall.

The right suprarenal gland is usually seen at the lowest part of this area of dissection, peeping through the peritoneum. On the other hand the exposure may be very niggardly, and it may be necessary to pack off or even withdraw part of the small intestine or colon from the abdomen, before sufficient access can be obtained.

The right splanchnic nerve is smaller and much more difficult to find than the left. It may be represented not by one trunk, but by two or three fine fibrils. The position and course is the same as for the contralateral nerve - downwards, forwards and medially above the suprarenal gland. The points/

points of the forceps left on the coeliac end of the cut left splanchnic nerve may here prove an invaluable guide to the position of the coeliac plexus and the right splanchnics. (Fig. 29)

In some cases, especially where the animal is fat, it may be impossible to identify the nerves at all, and in these cases it has been my custom to resect all the tissue covering the right crus of diaphragm and back wall muscles above the suprarenal, in the space between the mesentery of the duodenum and the portal vein.

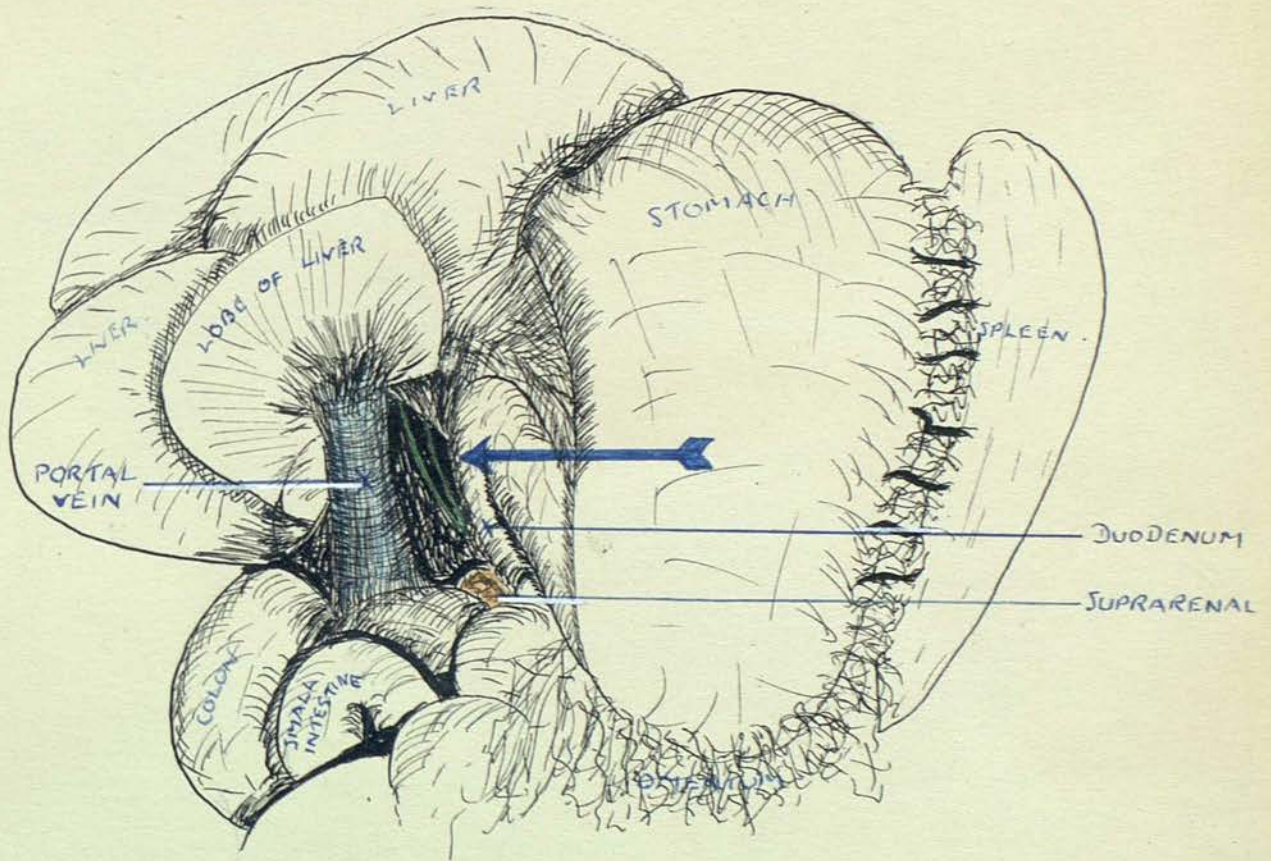
In favorable cases the nerve is caught between 2 pairs of artery forceps and a portion resected. It is advisable to ligate the ends before removing the forceps as an artery often closely accompanies the right nerve and is cut at the same time as the nerve.

Bleeding points, which may be quite troublesome, are either caught or controlled by gauze pressure.

When haemostasis is attained, packs and forceps are removed and the abdomen closed in layers. No dressing is applied.

The animals quickly recover, and their appetite and health appear quite normal within 3 days.

FIGURE 29.



OPERATIVE EXPOSURE OF THE RIGHT

SPLANCHNIC NERVE.

LIVER IS TURNED
UP AND TO RIGHT. BLUNT DISSECTION
IS PROCEEDED WITH IN SPACE BETWEEN
DUODENAL MESENTERY AND PORTAL VEIN.

Stage II. Construction of Gastric Pouch
with intact vagal nerve supply.

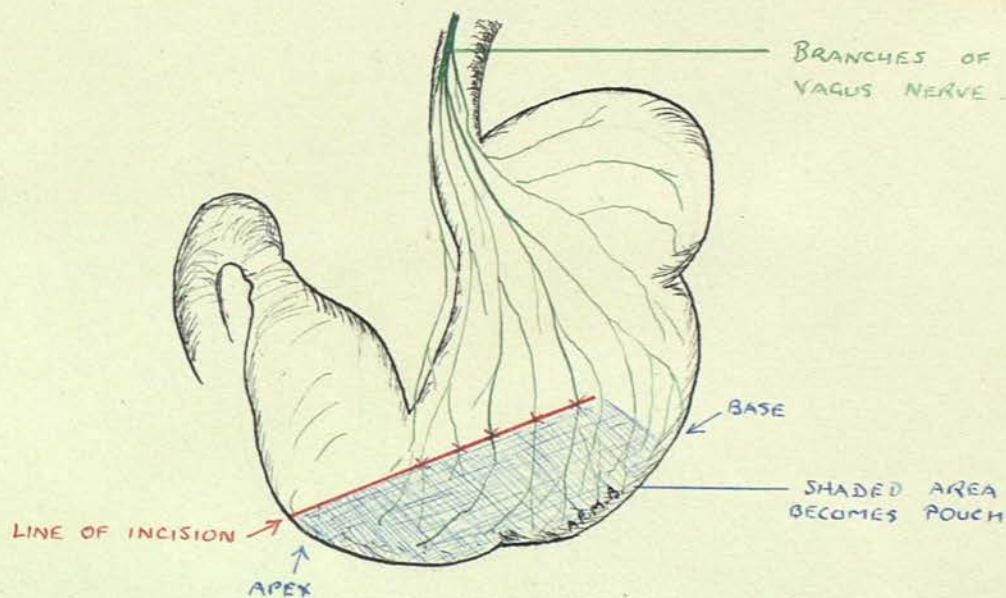
The so-called "Pavlov Pouch" met the requirements of the experiment to a certain extent. Indeed this pouch has apparently been accepted exclusively as the best (or only) one with nerve supply intact, and Pavlov's original technique has been slavishly followed by subsequent experimenters.

I constructed a few such pouches myself in cats, but came to the conclusion that however nice the operation looked in the diagrams usually given, the method was based on faulty anatomical data as far as the cat was concerned. Numerous vagal fibres were cut in the operation and only about one third of the pouch had an intact nerve supply. (Fig. 30)

Figs. 31 and 32 (drawn from actual dissections) show the distribution of the vagus to the stomach of the cat. Most of the nerves descend subserously over the stomach wall almost vertically or with only a slight obliquity, until they reach the level of the incisura angularis, and not along the greater curvature as the usual Pavlov diagram (for the dog) indicates. The Pavlov pouch operation therefore obviously cuts many of these vagal fibres and only a very few, right at the greater curvature itself, where the outer stomach wall is intact, escape.

After/

FIGURE 30.



INCISION FOR PAVLOV POUCH IN THE CAT

SHOWING NERVES CUT IN THE PROCESS,
ONLY A VERY FEW AT THE BASE OF
THE POUCH ESCAPE.

FIGURE 31.

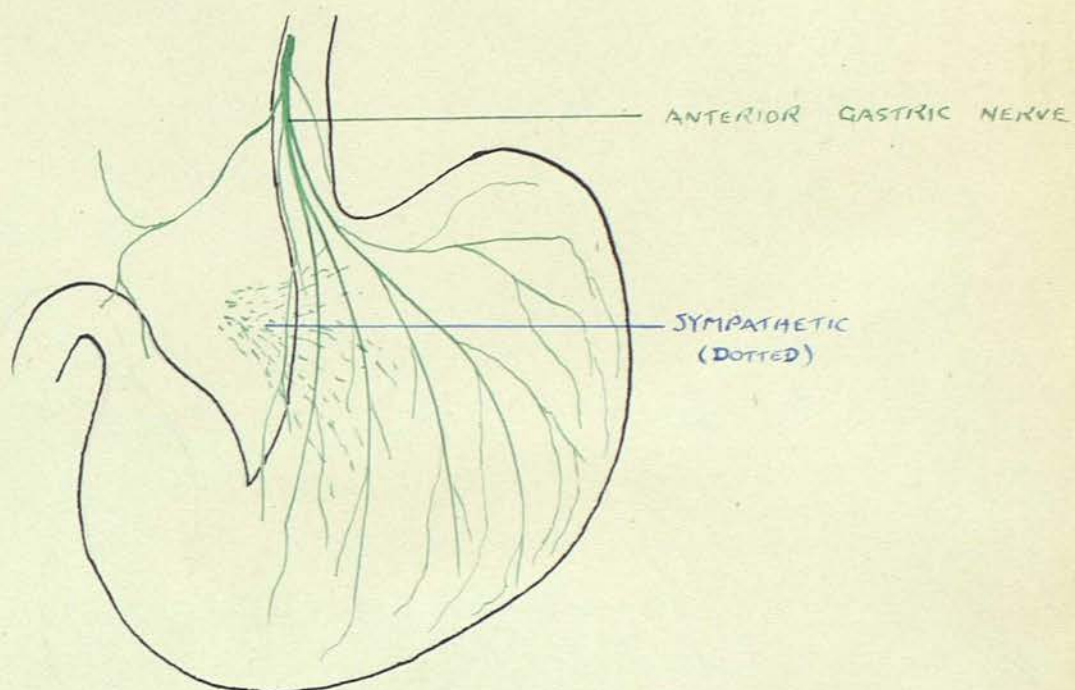
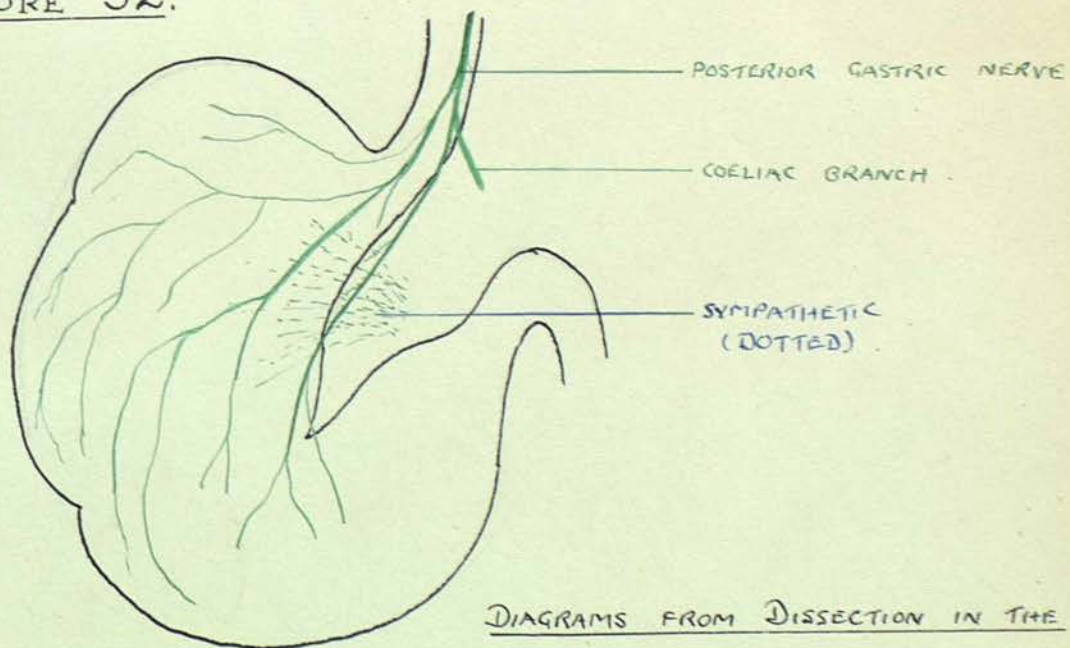


FIGURE 32.



DIAGRAMS FROM DISSECTION IN THE
CAT TO SHOW DISTRIBUTION OF THE
NERVES TO ANTERIOR AND POSTERIOR
ASPECTS OF THE STOMACH.

After discussing the above points with Mr W.A.D. Adamson, I constructed a gastric pouch using anterior stomach wall only, the base of the flap being as near the oesophagus as practicable, the apex at the lowest part of the stomach (See Fig. 33)

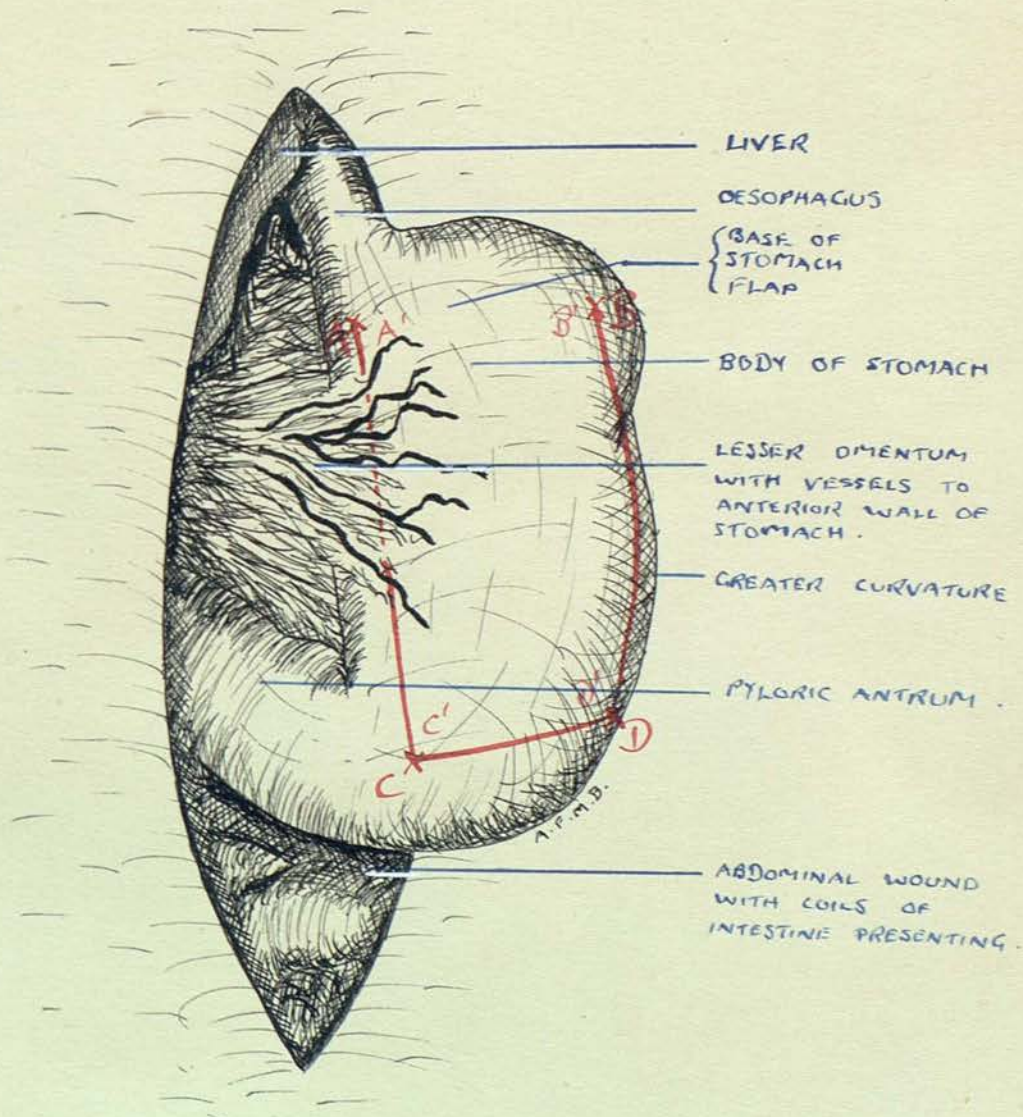
Approximately 3 weeks after splanchnic section has been performed, the abdominal wound is firmly healed. The animal is again put under open ether anaesthesia, and with all aseptic precautions, the abdomen is opened for a second time, on this occasion, through a median or left paramedian incision.

The stomach is withdrawn from the abdomen and packed round with moist warm swabs. 4 tissue forceps are placed on the serous coat at the following places on the anterior surface of the stomach: (A) near oesophagus just at lesser curvature, (B) at same level near greater curvature (C) on body of stomach about 1 cm. away from incisura angularis (D) at same level as (C) only on greater curvature (See Fig. 34).

With a sharp scalpel, the serous coat of the stomach is cut between the forceps, marking out a roughly rectangular flat with its base uppermost. Care is taken to avoid the vessels crossing the lesser curvature to supply the stomach. They are easily elevated from the stomach wall by blunt dissection, and the serous coat under cover of them then cut.

All/

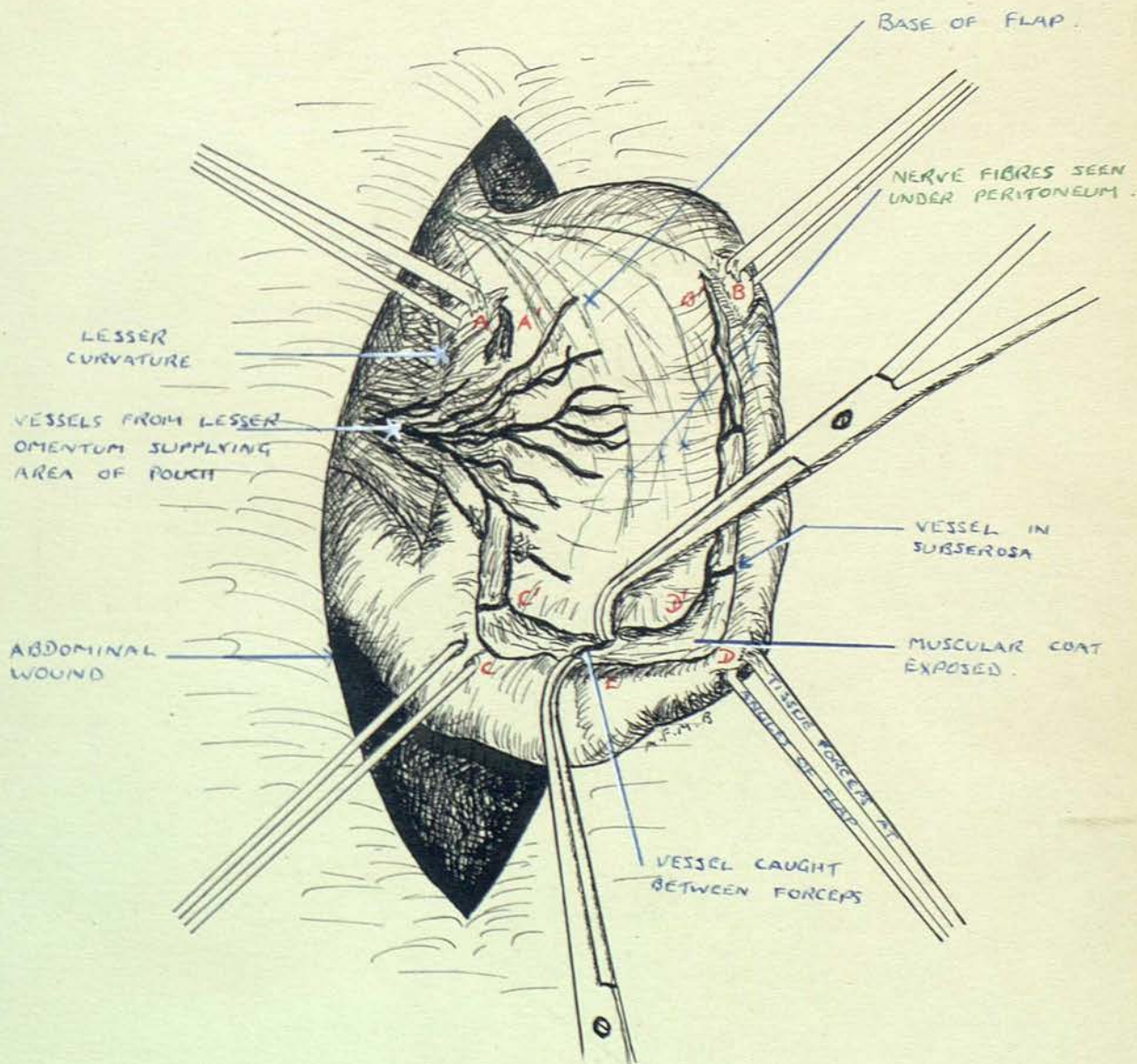
FIGURE 33.



ANTERIOR GASTRIC POUCH OPERATION.

STOMACH FLAP MARKED OUT, STOMACH
HAVING BEEN WITHDRAWN FROM ABDOMEN
THROUGH MEDIAN OR LEFT PARAMEDIAL INCISION.

FIGURE 34.



ANTERIOR GASTRIC POUCH OPERATION. (STEP I)

TISSUE FORCEPS AT ANGLES OF POUCH. PERITONEUM
INCISED. OBVIOUS VESSELS IN SUBSEROSA CAUGHT
AND TIED. LEASH OF VESSELS CROSSING LESSER
CURVATURE ELEVATED FROM STOMACH WALL AND
PRESERVED.

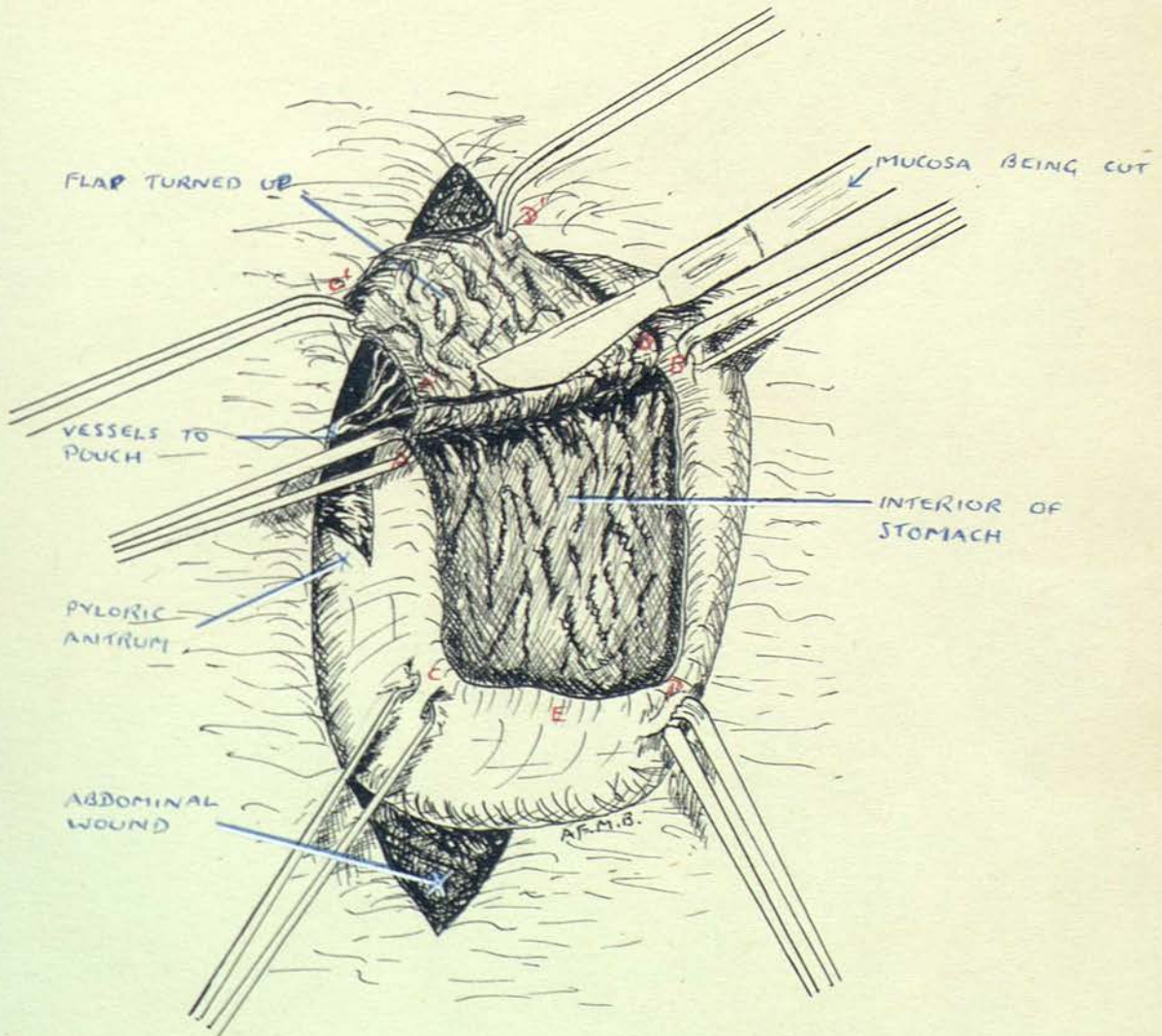
All obvious vessels running in the subserosa are caught between forceps, cut and ligated.

The lumen of the stomach is now opened by cutting the remaining coats at the side of the flap opposite to the base (Fig. 34 C D). Suction is used to empty the stomach of any contents, and then the 2 remaining sides of the flap are cut (Fig. 34 C A, D B) with scissors, care again being taken to preserve the vessels crossing the lesser curvature. Bleeding points at the cut edges of the stomach are caught in forceps. They are surprisingly few if the obvious vessels in the subserosa have already been dealt with as described.

The flap thus made is turned upwards and to the animal's right carrying its vessels with it, and leaving the cavity of the stomach exposed. The base of the flap is defined from the mucosal aspect and a light incision cutting the mucosa only is made across the base (Fig. 35 A B). By the aid of very fine dissecting forceps a narrow leaf of mucosa is dissected back from the cut on each side. The muscle layer, the subserous layer and the peritoneum are of course intact in the line of the mucosal incision, as are also the nerves which run either under the peritoneum in the subserous layer, or between the muscle coats.

The/

FIGURE 35.



ANTERIOR GASTRIC POUCH OPERATION.
(STEP II)

STOMACH OPENED AND FLAP THROWN UPWARDS CARRYING ITS
VESSELS WITH IT. MUCOSA AT BASE OF FLAP IS INCISED, BUT
MUSCULAR AND SEROUS COATS WITH THE NERVES RUNNING IN THEM
ARE LEFT INTACT.

The next step is to close the stomach. A continuous suture of fine catgut (No. 00 to No. 0000) is started at the middle of the mucosal flap nearest the oesophagus and the edges of the flap folded on themselves by means of the "loop on the mucosa" stitch. (Fig. 36)

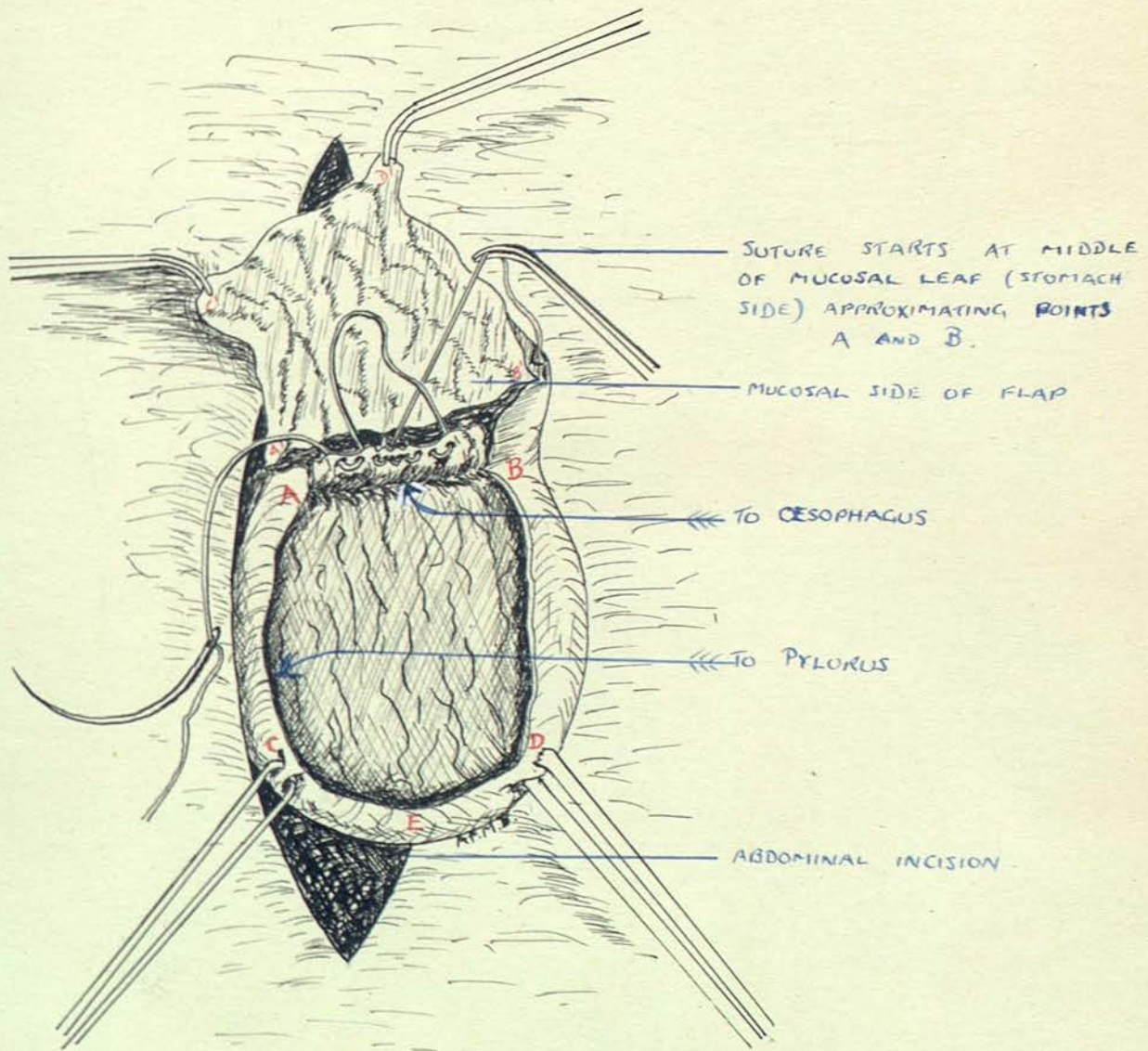
The points A B (Fig. 35) have now been approximated and the closure of the stomach is completed by through and through stitching taking in muscle and mucosa.

A similar procedure is adopted when making the pouch. A continuous catgut suture folds the edges of the remaining mucosal leaf (A'B') on themselves, and thereafter the suture is continued as a through and through stitch uniting the edges of the main flap (Fig. 37) A'C' to B'D'. An opening of about $\frac{1}{2}$ cm. diameter is left at the end of the pouch thus made.

The stitching is now completed by covering the suture line with peritoneum by means of a continuous Lambert stitch which starts at the lower end of the stomach, comes right up to what was the base of the stomach flap (A B) but is now pulled together, and passes on covering over the suture line of the pouch.

The lumen of the stomach is thus completely closed and the continuity of alimentary canal intact. The lumen of the stomach is separated by a double diaphragm/

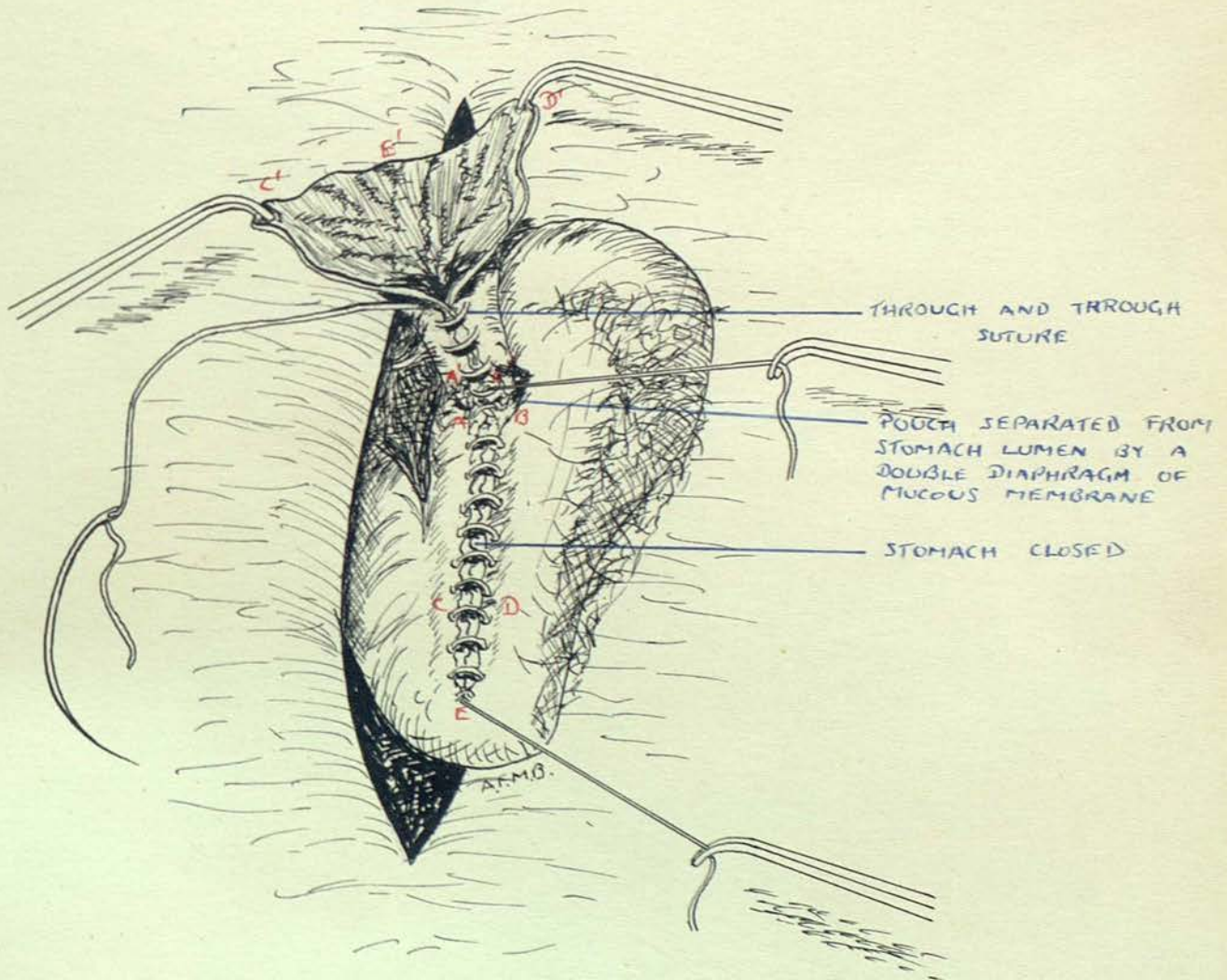
FIGURE 36.



ANTERIOR GASTRIC POUCH OPERATION.
(STEP III)

COMMENCING CLOSURE OF STOMACH, THE ELEVATED MUCOSA AT BASE OF FLAP IS DRAWN TOGETHER BY THE "LOOP ON THE MUCOSA" STITCH, THE REST OF THE STOMACH IS CLOSED BY A "THROUGH AND THROUGH" SUTURE FROM POINT AB TO E.

FIGURE 37.



ANTERIOR GASTRIC POUCH OPERATION.
(STEP IV)

STOMACH CLOSED. MUCOSAL LEAF ON POUCH SIDE OF BASE OF FLAP HAS BEEN DEALT WITH AS IN STOMACH CLOSURE (STEP III). A "THROUGH AND THROUGH" SUTURE NOW IS FORMING THE ISOLATED STOMACH POUCH.

diaphragm of mucous membrane from the lumen of the pouch (Fig. 38)

The operation is completed by making a stab incision from the inside in the left side of the cat's abdomen and pulling the mouth of the pouch through. (Fig. 39)

Forceps and packs are removed, haemostasis secured and the abdomen closed in layers. Finally the muscle and serous coats of the mouth of the pouch are fixed by 2 single stitches to the muscle and peritoneum at the edge of the stab wound. The skin around the opening of the pouch is smeared with Zinc Oxide Paste and this is repeated daily.

Summary of Results: Series II.

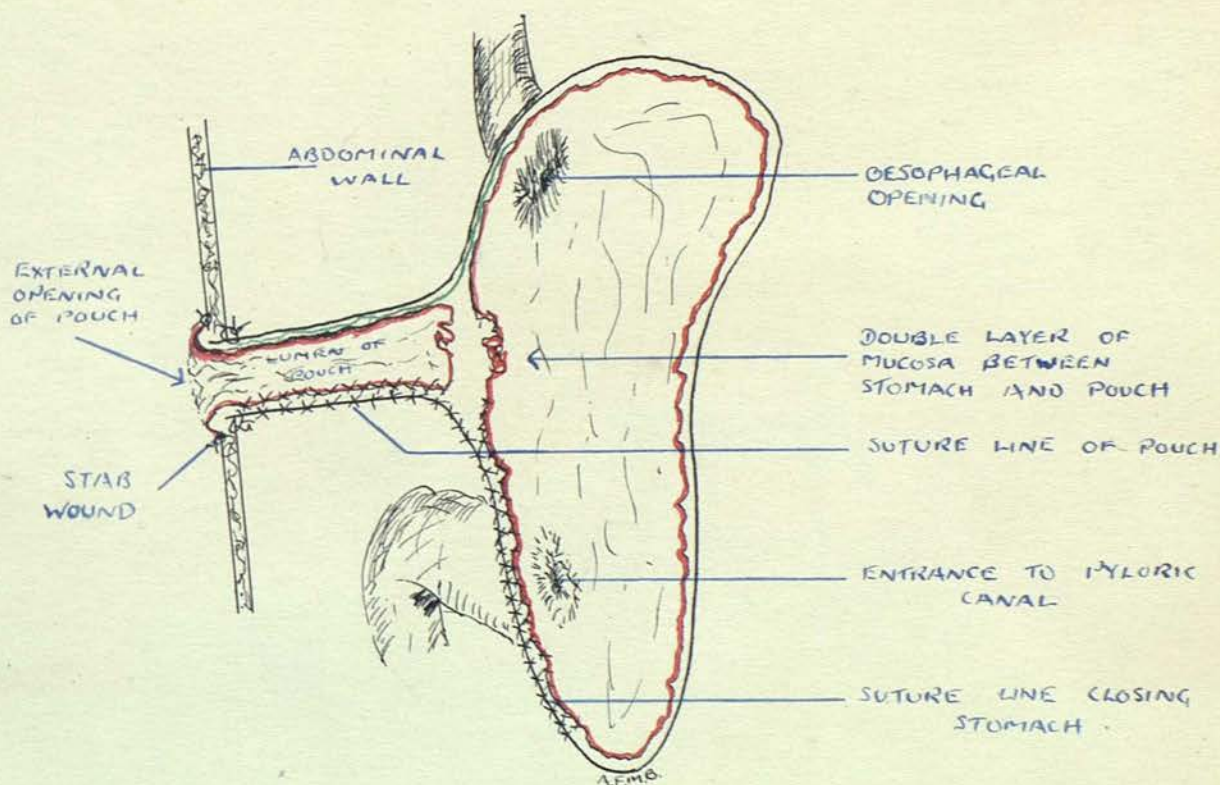
(Indirect Stimulation of Vagus)

Up to the time of writing only eight experiments had been completed, so this report is only of a preliminary nature.

Group I. (Experiments performed as described).

1. Subacute ulcer at apex of pouch running into suture line (Cat No.1.).
2. Chronic ulceration (not typical) at mouth of pouch with perforation of mucous/skin line.
Peritonitis. Terminal acute duodenal ulcer with haemorrhage. (Cat No.4)

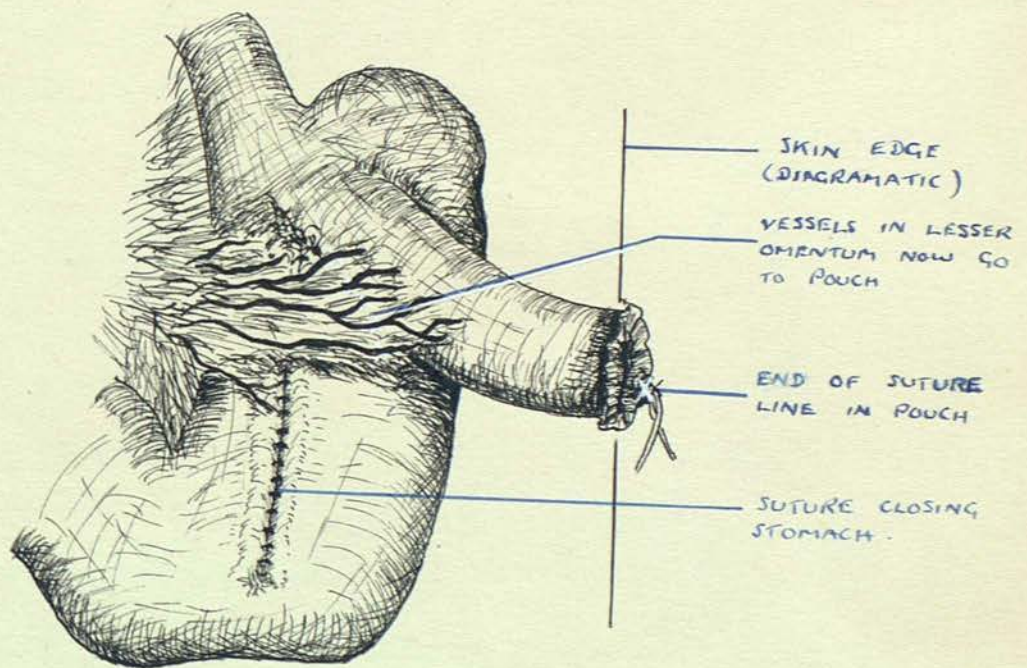
FIGURE 38.



ANTERIOR GASTRIC POUCH OPERATION

CORONAL SECTION THROUGH COMPLETED POUCH AND
CLOSED STOMACH (DIAGRAMATIC) TO SHOW DOUBLE
DIAPHRAGM OF MUCOSA SEPARATING LUMEN OF POUCH
FROM THAT OF STOMACH. NERVES TO POUCH ENTER
EXTRA - MUCOSALLY AT BASE AND ARE INTACT.

FIGURE 39.



ANTERIOR GASTRIC POUCH OPERATION.

THE FINISHED POUCH . THE SUTURE LINE OF
THE STOMACH CAN BE SEEN : THAT OF THE POUCH
IS HIDDEN IN THIS VIEW .

3. Superficial ulcer at apex of pouch within 36 hours of operation. (Cat No. 5)
4. Typical chronic ulcer with perforation. (Cat No. 7).
5. Typical chronic ulcer. (Cat No. 9).
6. Ovoid ulcer at skin/gastric mucosal edge. Perforation of base of ulcer with adhesion to liver and localised peritonitis. (Cat No. 10).
7. Subacute ulcer in middle of suture line. The ulcer was perforated and adherent to the spleen. Localised peritonitis with dense adhesions. (Cat No. 12).

Group II. (Control).

Here the right splanchnic nerve or one of its roots remained intact.

1. No ulcer. (Cat No. 2).
2. No ulcer. (Cat No. 6).
3. No ulcer. (Cat No. 8).
4. No ulcer. (Cat No. 11).

Group III. (Control).

Several experimental bilateral splanchnic sections were performed in cats without the addition of a gastric pouch. These animals remained well and no ulcer developed even after several months. This observation is in accordance with that of many others, using both cats and dogs.

Fuller descriptions of the various findings in individual experiments now follow.

PROTOCOLS OF EXPERIMENTS.EXPERIMENT 1.

(One stage operation). 15.3.38.

Splanchnic Section easily performed.

Anterior Gastric Pouch made. There was slight soiling of the peritoneum when the animal suddenly strained as the anaesthetic became too light. Some mucoid stomach contents got on to the edge of the abdominal wound.

Post-operative Period.

The animal remained fairly well for one week, taking about half its normal food, and then died suddenly overnight.

Post-mortem Summary. 22.3.38.

There were adhesions and sero-pus under the diaphragm. There was an ulcerated area of about $\frac{3}{4}$ cm. in diameter near the fundus of the pouch. The ulcer had slightly rolled edges which felt a little harder than the rest of the mucosa. The mucosa around showed slight congestion. The base of the ulcer was rather sloughy but had unfortunately run into the suture line.

Remarks.

The ulcer had some resemblance to the sub-acute/

subacute gastric ulcer in man, but the fact that a recent suture line ran into the ulcer suggests the definite possibility of faulty technique in stitching being one of the main factors in the production of this ulcer.

EXPERIMENT 2.

One Stage Operation. 24.3.38.

Bilateral Splanchnic Section.

Anterior Gastric Pouch made.

Post-operative Period.

Recovered completely in 3 days. Appetite and general health good till intervention of respiratory infection and sudden death on 17.4.38.

Post-mortem Summary.

Bronchopneumonia.

Stomach and Pouch both well healed and firmly separated from each other. Mucosa of stomach normal; that of the pouch was smoother than usual for stomach tissue, and slightly congested. There were no ulcers.

Remarks.

On completing the post-mortem, the right splanchnic nerve appeared still to be intact. Only a small root must have been cut at operation!

EXPERIMENT 3.

Operation (One Stage). 31.3.38.

Bilateral Splanchnic Section.

Anterior Gastric Pouch of large dimensions
made with sacrifice of the lesser omental artery.

Post-operative Period.

Never truly recovered.

Died 3.4.38.

Post-mortem Summary.

Gangrene of Pouch with foul peritonitis.

Remarks.

In the operations hereafter, great care
was taken to preserve the vessels crossing the lesser
curvature, in order to retain an efficient blood
supply for the pouch.

EXPERIMENT 4.Operation 1st Stage. 18.4.38.

Bilateral Splanchnic Section. Region of Right crus of diaphragm cleared by block dissection. Good recovery.

2nd Stage. 3.5.38.

Anterior Gastric Pouch made, retaining the vessels crossing the lesser curvature.

Post-operative period.

Well until 13.5.38 when cat began to go off its food. Soon developed bloody diarrhoea. On 16.5.38 it vomited some "coffee-ground" material giving a positive guaiac test. Died on 17.5.38.

Post-mortem Summary.

The stomach contained dark brown semi-fluid material. The first 1" of duodenum was packed with clotted blood. The mucosa of the duodenum was congested and an ulcer measuring 6 x 3 m.m. was found in the wall.

The skin round the pouch was excoriated, and the mouth of the pouch itself exhibited an ovoid ulcer measuring 10 x 6 m.m. It was surrounded by hard fibrous tissue and the junction between skin and gastric mucosa was deficient at one part through which/

which the peritoneal cavity communicated with the exterior. The peritoneal cavity was filled with a very foul discharge.

Remarks.

This result was more hopeful with regard to ulcer production. The fact however, that the gastric ulcer occurred at the very skin edge brings complications into the aetiological inference, because the skin was definitely excoriated and infected, so that the ulceration may well have spread from the skin in the first instance.

EXPERIMENT 5.

Operation 1st Stage 18.4.38.

Bilateral Splanchnic Section after which the animal quickly recovered.

2nd Stage 4.5.38.

Anterior Gastric Pouch was made. During operation however, the animal stopped breathing and artificial respiration had to be given.

Post-operative period.

The animal seemed to recover all right and was running about its cage the next morning. During that day however it suddenly lay down and died.

Post-mortem Summary 5.5.38.

Collapse of lungs seemed to be present. There were numerous hyperaemic spots in the pouch and a small superficial erosion near the apex. No other abnormality was found.

Remarks.

The time of observation was much too short for any deductions regarding chronic ulceration to be drawn. Illustration of how quickly superficial erosion may take place after operation was supplied.

EXPERIMENT 6.Operation 1st Stage 19.4.38.

Bilateral Splanchnic Section performed.

The right nerve was small and access rather difficult owing to large liver. Recovered well from 1st stage.

2nd Stage 10.5.38.

The wound of the first operation was well healed. Anterior gastric pouch was successfully made, although at one time the animal had a great excess of secretion in its throat with consequent respiratory embarrassment and poor oxygenation.

Post-operative Period.

The animal recovered well, and retained its good health. About 3 weeks after the 2nd operation the skin round the mouth of the pouch became very excoriated, and began to break down. The animal was killed on 6.6.38.

Post-mortem Summary 6.6.38.

No ulcer was present. The stomach and pouch were both well healed.

One root of the right splanchnic nerve was still intact.

EXPERIMENT 7.

Operation 1st Stage 19.4.38.

Bilateral Splanchnic Section performed without much difficulty.

2nd Stage 11.5.38.

Previous wound so well healed that it scarcely could be distinguished from the inside of the abdomen. No adhesions.

Anterior Gastric Pouch made.

Post-operative Period.

The animal quickly recovered and remained well. Although the cat was still in good general health on 2.6.38 there was an oozing of blood from the mouth of the pouch. The skin around it also was beginning to break down. The cat was killed on 6.6.38.

Post-mortem Summary 6.6.38.

On opening the abdomen, the peritoneal cavity was found to be matted with adhesions, especially in the upper part.

The stomach mucosa was normal and the suture line well healed. The mucosa of the pouch looked normal but at the apex there was a typical small chronic ulcer with radiate strands of thickened tissue running out from the ulcer. The tissues round about it felt much harder than the rest of the pouch or stomach. The ulcer had perforated and was adherent to the/

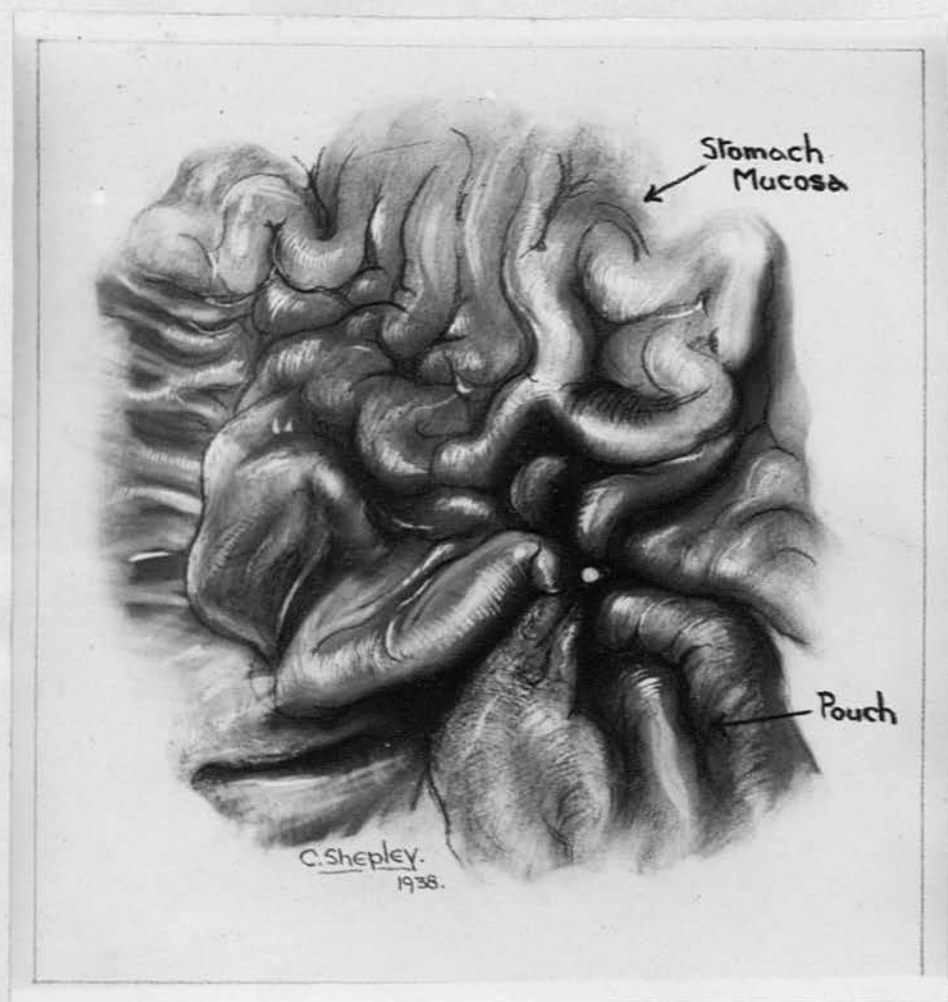
the liver, which organ formed its base. (Fig. 40).

Both splanchnic nerves were found to be cut.

Remarks.

A very typical chronic "peptic" ulcer had formed in this experiment - exactly what it was hoped would happen, the experiments having been designed to produce this.

FIGURE 40.



A DRAWING OF THE CHRONIC GASTRIC

ULCER OBTAINED IN CAT NO. 7, (SECOND

SERIES). TO SHOW THE ULCER, BOTH

POUCH AND STOMACH HAVE BEEN CUT OPEN.

EXPERIMENT 8.Operation 1st Stage 4.5.38.

Left splanchnic section easy. Right nerve difficult to expose because of fixed, low lobe of liver. This lobe was mobilised by cutting some adjuvant peritoneal attachments. Two fine nerves crossing medially, downwards and forwards above the right suprarenal gland were resected. The right crus of diaphragm was also cleared of covering tissue.

Recovery rapid.

2nd Stage 25.5.38.

Would well healed. Few adhesions. Anterior Gastric Pouch made.

Post-operative period.

Recovered quickly and remained well for a week, but then began to go off its food slightly. Slight excoriation of the skin round the mouth of the pouch. Killed 6.6.38.

Post-mortem Summary.

Mucosa of stomach and pouch both healthy. Suture line healed. No ulcers.

One root of right splanchnic nerves was still intact.

EXPERIMENT 9.

Operation 1st Stage 12.4.38.

Bilateral splanchnic section performed.

Operation 2nd Stage 26.4.38.

The animal was in good health. On opening the abdomen a few adhesions were seen attached to the stomach. These were cut between ligatures and an anterior gastric pouch then easily constructed.

Post-operative period.

The cat made a rapid recovery and remained well until it was sacrificed on 7.7.38.

Post-mortem Summary.

There was a large round ulcer in the pouch about a third of an inch in diameter. There was not a great deal of fibrosis, but some short firm radiating stria could be distinguished. The edges of the ulcer were moderately indurated and the base was sloughy. There was a strong resemblance to a chronic gastric ulcer in man.

Both splanchnic nerves had been cut.

FIGURE 41.



PHOTOGRAPH OF A CHRONIC ULCER

DEVELOPED IN THE GASTRIC POUCH

OF CAT NO. 9.

EXPERIMENT 10.Operation 1st Stage 25.4.38.

Bilateral splanchnic section. The right nerve was very small so a block dissection of the loose tissues in front of the back wall to the right of the coeliac plexus was done as well.

Operation 2nd Stage 24.5.38.

Anterior gastric pouch constructed.

Post-operative period.

Recovery was rapid. Health was maintained till the beginning of July when some sepsis at the edge of the fistula was noted, and the cat went off its food. It was killed on 7.7.38.

Post-mortem Summary.

There was an ovoid ulcer at the edge of the fistula with erosion of both skin and mucosa. The base of the ulcer had perforated and was adherent to the liver. There were matted adhesions round the area of perforation.

Both splanchnic nerves had been cut.

EXPERIMENT 11.Operation 1st Stage 10.5.38.

Bilateral splanchnic section performed with considerable difficulty owing to the stomach (containing a hair ball) ballooning through the wound and over the field of operation.

Operation 2nd Stage 31.5.38.

Anterior Gastric pouch made, hair ball being removed from the stomach in the process.

Post-operative period.

The cat recovered its good health in a few days. It was sacrificed on 7.7.38.

Post-mortem Summary.

No ulcer was discovered. On examining the condition of the splanchnic nerves it was found that the right splanchnic still remained intact, obviously having been missed in the first stage of the operation.

EXPERIMENT 12.Operation 1st Stage 13.5.38.

On opening the abdomen a huge stomach presented in the wound, as, unfortunately by some mischance, the animal had not been starved long enough before operation. I resected a piece of the left splanchnic nerve in the usual manner, but the right was quite inaccessible. The abdomen was then closed.

Operation 2nd Stage 3.6.38.

The right splanchnic nerve was first cut and then with some difficulty, owing to the presence of adhesions from the previous operation, a gastric pouch made.

Post-operative Period.

The animal recovered and remained in good health until sudden death overtook it on 13.6.38.

Post-mortem Summary.

The skin at the fistulous opening was breaking down. Inside, there were numerous adhesions between wound, pouch and spleen. A small sub-acute ulcer was present about half way down the suture line of the pouch. This ulcer had perforated and was adherent to the spleen. The rest of the suture line was well healed.

Both splanchnic nerves had been cut.

Conclusions from experiments. Series II.

Although the series is a small one, some definite results have been attained.

As has already been shown, if the neutralizing and diluting effect of food and duodenal secretions is diverted from the stomach the strength of the hydrochloric acid in contact with the gastric mucosa rises considerably (to 0.5%, Page 37). This happened in the experiments of Group 2 (see pages 145 & 146) where an anterior gastric complete with both vagal and sympathetic (through right splanchnic nerve) nerve supply was made. Yet no ulcers developed.

In Group 3 where both splanchnic nerves were cut causing a sympathetic denervation of the stomach, a relative vagal overaction is attained, but the effects of this are damped by the neutralizing and diluting properties of the food and duodenal secretions. In this group also no ulcers developed. These two groups therefore serve as controls.

But when a gastric pouch with vagal nerve supply intact, but deprived of sympathetic impulses is constructed as in Group 1, ulcers develop. In each of the seven experiments in which this was done some pathological condition developed - two cases of typical chronic ulceration, one with perforation; two cases of subacute ulcer at suture line, one perforated; two cases of indurated ulcer at mucous/skin edge actually eroding the mucosa, both perforated into the peritoneal cavity; and one acute superficial/

superficial ulcer in a cat which died within 36 hours of operation.

The indication from these few experiments is therefore that the great causative factors in "peptic" ulceration is the combination of Relative Vagal Over-action and Hyperchlorhydria.

Another favorable point in the results of the experiments is the fact that ulceration, especially chronic or subacute, and perforation of the peritoneal cavity are particularly difficult to produce in the gastric mucosa of the cat; neither does this animal suffer spontaneously from an such form of ulceration.

X. CHRONICITY IN GASTRIC AND DUODENAL ULCER.

Acute ulceration of the stomach is a common occurrence and is associated with a variety of general conditions. Such ulcers have been demonstrated pathologically at post-mortem (where they have to be distinguished from agonal changes), by the gastroscope, and by deduction from clinical findings. Shallow duodenal scars are also frequently found post-mortem. (64) (76)

Experimentally they may be produced in about 50 different ways of which the following are the main methods.

Lesions of the Central Nervous System,
 Certain lesions of the Vagus Nerves,
 " " " " Splanchnic Nerves,
 Trauma to the Stomach,
 Local Embolic Circulatory Disturbances,
 Ingestion of Bacteria,
 Intravenous injection of bacterial toxins,
 Injection of chemical substances into the stomach
 e.g. Silver nitrate, adrenalin,
 Intravenous injection of poisons and autolytic
 toxins,
 Cutaneous burns,
 Removal of adrenal glands. (33) (102)

It is a legitimate assumption that a chronic ulcer has as its beginning one of these acute ulcers. The cause of such chronicity is very difficult, indeed impossible with the data at hand, to decide. Several of the more important helpful considerations however may be put down. The first of these is hypersecretion, hyperacidity and pylorospasm due to vagus overaction. (48).

The localisation of chronic ulcers in the region of the lesser curvature is a finding which cannot be discarded. Both macroscopically and histologically a great multiplicity of nerve fibres are collected in the region of the lesser curvature, very many more than in any other part. Furthermore quite large nerves are often seen running across the floor of an ulcer (138) (139) open to the assaults of all the gastric contents. It is easily seen how such an occurrence could cause vagal irritation and set up a "vicious circle".

Local circulatory disturbances in the stomach mucosa (Virchow) also have to be considered, either of the nature of ischaemia or of dilatation, extravasation and consequent thrombosis. It is well known that the autonomic nerves control vasomotor tone and such changes as the above may well be caused by nerve influences, thus this local explanation of ulcer (80).
held/

held for so long as the primary cause of ulcer may not only be reconciled but explained by the neurogenic theory.

Gastritis and Chronic infection must be mentioned (12) (77). Although they doubtless work by direct noxious action on the tissues it is conceivable that their effects are consummated through the production of a neuritis in the nerves of the stomach walls with consequent trophic disturbances.

Finally, recurrent traumata must deleteriously affect the mucosa. The dynamics of the stomach are such that contents, whether it be hyperacid secretion when "at rest" or coarse or otherwise irritating food when eating, are all forced towards the magenstrasse and then propelled against the first part of the duodenum - the very places where ulcers flourish.

A publication on chronic gastric ulcer of great interest has appeared just recently (140). The administration of cincophen in toxic doses to animals has long been known to produce acute gastric or duodenal ulcer. It now appears that if the administration of this drug is continued, the animals become tolerant to it and appear to lose the signs of toxæmia which they showed at first.

In a few weeks, ulcers comparable to human chronic ulcer, develop in the lesser curvature area following/

following on the original acute ones. These ulcers remain unhealed as long as the cincophen is continued but heal within 3 - 4 weeks of the stoppage of the drug.

No direct analogy can be drawn with ulcers in the human being, where cincophen obviously is not the cause of the ulceration, yet the observations are extremely interesting and may form a most crucial fact when confirmed and the exact significance of the findings understood.

XI. CONCLUSION.

In this thesis I have put forward the plea that the cause of the distressing conditions of irritable "peptic" ulcer and the gastric neuroses is a neurogenic one. At times I have been lead away from the main track of my argument into discussions of the general aetiology and clinical and pathological findings of related conditions; but that was inevitable in such a debatable and complicated subject. It is not possible yet to come to a definite conclusion, but in my own mind at least, I am convinced that understanding is clearer, and the meaning of certain findings more obvious in the light of the neurogenic theory, than in that of any other. Much work and study must yet be given to the whole subject before the theory is finally either discarded or finds a general acceptance.

However, I have summarised my main deductions and conclusions from a study of the literature and from my own personal observations, both clinical and experimental. None the less, it must be understood that the neurogenic approach to the subject of peptic ulceration is still a comparatively new one and the consideration of the results of future experiments may well cause modification of some of the conclusions hereinunder put forth.

1. The human stomach gains its nerve supply from two sources, the vagus (parasympathetic) and the sympathetic (through the coeliac plexus).
2. The gastric vagal branches are very constant in position and distribution and the main branches can be identified at operations on the stomach.
3. Relative overaction of the vagus produces hypersecretion, hypermotility, hyperacidity and pylorospasm.
4. The main factor in the causation of "peptic" ulceration and the gastric neuroses is the combination of Relative Vagal Overaction and Hyperchlorhydria.
5. Relative Vagal Overaction in the human being may be either constitutional (inherited) or acquired.
6. Hyperchlorhydria is principally and in most cases the direct result of vagal stimulation. The usual level of gastric acid may be raised to an extent the absence of by the diluting and neutralizing factors in the diet, and/or derangement of the internal chemical mechanism for the maintenance of normal gastric acidity.
7. A reasonable new assay of the treatment of duodenal ulcer without stenosis in a young person, and of the gastric neuroses, would be
 - a. by exhibition of the newer drugs of the belladonna series - ephedrine, or especially benzedrine, which produce a relative diminution of parasympathetic activity;
 - b. /

- b. by exhibition of sedatives, especially pheno-barbitone and the bromides, which reduce autonomic activity as a whole;
- c. by vagal neurectomy, by resecting a small length of anterior gastric nerve, and of the posterior gastric nerve after it has given off its large right branch (which goes to supply the small intestine). The approach is through a high paramedial incision into the left xiphi-costal angle and exposure can easily be obtained as described by Latarjet (page 79, Figs. 2, 11, 12).

The operation is feasible, and quite quickly performed; it does not entail the shock and considerable anaesthetic duration of the usual abdominal operation where much handling of the gut takes place; it is not mutilating as in the partial gastrectomy often advised; and should the operation fail to produce the expected results, the application of the routine medical treatment is not precluded, neither is the performance of gastroenterostomy or partial gastrectomy should such a major surgical procedure by any chance be deemed advisable.

Finally I have but to offer my thanks and acknowledge my debt to all those who have helped and encouraged me in my work; to the various Honorary and Surgeons Physicians with whom I have discussed my problems, in/

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abstracts, particularly in the case of German
authors.

REFERENCES, Alphabetical.

<u>Name of Author.</u>	<u>Number of Serial Reference.</u>
Abel	27
Adamson	40, 136
Alvarez	24, 37, 122, 127, 132
Aron	81
Arndt	73
Askanazy	139
Babkin	42
Baird	51
Banting	134
Barron	107
Beattie	17
Beneke	75
Bennett	121
Berg	115
Bergh	126
von Bergmann	10, 128
Best	33
Bircher	109
Boldyreff	49
Bollmann	140
Bolton	84, 50
Bowie	56
Brown	106
Campbell	51
Cannon	88
Carlson	89

<u>Name of Author.</u>	<u>Number of Serial Reference.</u>
Curtis	107
Cushing	15
Dale	34
de Vecchi	103
Dible	138
Dickinson	118
Dogeil	28
Dragstedt	43, 44, 46, 47
Draper	123
Duncan	38
Durante	101
Editor, B.M.J.	87
Edmunds	70
Eppinger	9
Ettinger	134
Exner	108
Farrell	68
Fauley	129
Feldmann	99
Flint	105
Foster	54
Friedenwald	99
Gask	137
Gaskell	6, 30
Goldberg	133
Goodhart	50

<u>Name of Author.</u>	<u>Number of Serial Reference.</u>
Greggio	100
Gunn	70
Gutzeit	65
Hall	134
Hart	76
Hartridge	21
Hartzell	104
Hearn	51
Heslop	16
Hess	9
Hill, F.C.	116
Hill, J.	119
Hoffman	3
Howes	48
Hughson	95
Hurst	12, 64
Ivy, A.C.	68, 69, 126, 129
Jamieson	18
Johnson	36
Katz	32
Keith	23
Keller	67
Keppich	72
Klein	26
Kollman	4
Könnecke	93
Konjetzny	63

<u>Name of Author.</u>	<u>Number of Serial Reference.</u>
Lander	124
Langley	7, 118
Latarjet	11
Lewisohn	111
Lim	31
Litthauer	90
Lorenzi	96
Loucks	135
McCann	53
McCarthy	69, 116
McCrea	13, 19, 66
McLagan	124
McSwiney	35, 66
Mann	57, 140, 133
Martin	83
Matthews	45, 46
Möller	1
Moll	105
Morton	102
Müller	29
Muir	79
Myerson	120
Neuman	60
Nieden	92
Norrish	20
Openchowski	25
Ophuls	98

<u>Name of Author.</u>	<u>Number of Serial Reference.</u>
Orator	33
Orndorff	126
Orr	86
O'Shaughnessy	85
Pavlov	41
Pulvertaft	71
Rössle	8
Rokitansky	2
Rosenow	77
Ross	137
Ryle	14, 121
Sandweiss	82
Schiassi	110
Schwarzmann	108
Seely	113
Shay	32
Shloss	32
Smidt	112
Somervell	86
Stahnke	130
Stalker	140
Steinthal	117
Stewart	64
Stierlin	91
Stopford	66
Swan	5

<u>Name of Author.</u>	<u>Number of Serial Reference.</u>
Thompson	125
Todd	131
Touraine	123
Vanzant	122
Vaughan	44
de Vecchi	103
Vedova	101
Vineberg	56
von Bergmann	10, 128
Watanabe	94
Weiss	59, 81
Wilhelmj	116
Wilkie	39, 78, 80
Williamson	57
Winkelstein	114
Winwarter	74
Wollard	20
Wright	61
Wu	58
Wylie	55
Yesko	52
Yzeran	97
Zollinger	113
